OGRESS IN VENEREOLOGY

BY

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s is intended as a book for the venereologist and a work of reference those who write on the venereal diseases It is a summary, with over)0 references, of the more important progress which has occurred since rld War II Apart from the discovery of the use of penicillin which nediately preceded them, these years have heralded the most striking ances in both the diagnosis and treatment of these disorders Written 3ritain, it thus contains a number of continental references and views ch do not always succeed in intruding into the American literature

t is not intended as a manual for the student or general practitioner hing to grasp the essentials of the management of the venereal diseases hese aspects are covered by the author's *Textbook of Venereal Diseases,*

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ıers along with the others He has allowed events to speak for themves, rather as a number of dots on graph paper, some wide of the mark, ılly form into a discernible pattern The references refer essentially to year 1946 and after, but the edges of distinction with the past and with lateral specialities have been toned down by the addition of a number others In their presentation the abbreviations of the *World List of ientific Periodicals* have been generally adopted, although on occasion ne words have been spelt out more fully when it was felt, by so doing, ıt the meaning would be made more clear

An attempt has been made to include as many of the important referces as possible in as small a space as is consistent with maintaining a herent narrative for those who desire to read the book for its own sake so to strike a balance between the two alternative criticisms of works of ıs sort, namely either that the author has been too uncritical in including o many references, or that he has shown personal prejudice or laziness giving too few Some undeliberate omissions there must be and due ologies are made to those concerned

Today, modern methods of treatment and contact tracing applied by e venereologist, and the mass use of penicillin by the general practitioner, ıve reinforced the usual post-war decline in the incidence of the venereal seases Indeed early syphilis seems already to be under control However, this is no moment for any relaxation of effort for the more difficult ıases lie ahead From now onwards we may expect a considerable num r of missed cases of syphilis contracted during the war years to become ›parent We must try and unearth these before they become symptomatic

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the last five years I have written annual surveys of the World's rature in the *Bulletin of Hygiene* under the title 'Perspectives in iereology' * Gratitude is wholeheartedly expressed to Dr Charles lcocks, the Editor of the *Bulletin of Hygiene*, for the care he has taken their presentation, and for his permission that they might form the leton of the present volume

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Finally I would like to pay tribute to the inspiration, help and—above ll—encouragement of the late Dr G M Findlay, whose death regret-ıbly occurred during 1952

* *Bull Hyg , Lond* (1948) 23, 133–44
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To

GEORGE MARSHALL FINDLAY

CONTENTS

CHAPTER I

GONORRHŒA

A. GENERAL

GONORRHŒA is still a prevalent disease although its incidence in Britain and the U S A has declined since the war. It has, however, ceased to be a serious illness, for ev useful in its treatment, the wide t a relatively trivial disease once at strains of gonococci will develop which are resistant to all of the effective antibiotics. It is conceivable, therefore, if contact tracing methods are intensified, that it may *ultimately* become comparatively uncommon in some parts of the world, although with its short incubation period it is not so amenable to control as syphilis, and such an outcome will take considerable time yet.

TABLE 1

CASES OF GONORRHŒA REPORTED FROM THE VENEREAL DISEASES CLINICS OF ENGLAND AND WALES

(Figures from Report of the Ministry of Health, H M Stationery Office, London)

Year	*Male*	*Female*	*Total*
1932	28,179	7,677	35,856
1933	29,169	8,583	37,752
1934	28,787	8,199	36,986
1935	27,506	7,732	35,238
1936	28,137	7,715	35,852
1937	29 250	7,787	37 037
1938	27,947	7,746	35,693
1939	24,811	6,489	31,300
1940	21,057	5,882	26 939
1941	20 572	7,314	27,886
1942	17,956	8,413	26,369
1943	18,215	10 043	28,258
1944	16,629	10,646	27,275
1945	21,280	11,603	32,883
1946	36,912	10,431	47,343
1947	29,647	7,019	36 656
1948	25 006	5,306	30,312
1949	20 366	4,121	24,487
1950	17 007	3,487	20,504
1951	14,975	3,089	18,064

The accompanying graph sho

marked fall from the war time peaks, and that the numbers of new cases reported from the clinics of England and Wales are below the 1941 figures

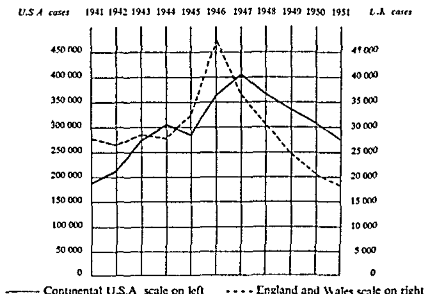


FIG 1—POST WAR TRENDS IN INCIDENCE OF GONORRHŒA—CONTINENTAL U.S.A AND ENGLAND AND WALES

(*Ministry of Health London and United States Public Health Service figures*)

U.S.A fall from 1947 peak = 32.5 % in 4 years
U.K fall from 1946 peak = 61.8 % in 5 years

FIGURES FROM WHICH GRAPH IS COMPILED

	U.S.A	U.K		U.S.A	U.K		U.S.A	U.K
1941	191 306	27 886	1945	284 994	32 883	1949	331 661	24 487
1942	212,384	26 369	1946	364 853	47 343	1950	303 992	20 504
1943	275 648	28,258	1947	400 659	36 656	1951	270 448	18 064
1944	300 585	27 886	1948	363 014	30 312			

B DIAGNOSIS OF GONORRHŒA

(1) Clinical

The pathology of gonorrhœa has been discussed by Harkness (1948). Van Spanje (1947) reported minor degrees of liver disturbance in 28 cases of acute uncomplicated gonorrhœa in 27 males and 77 females subjected to Quick's hippuric acid test

Nicol (1948) drew attention to the frequency with which the rectum is affected in women. Of 74 females tested, gonococci were isolated from the rectum of 26 and pus cells without gonococci in 14 others. Baranovskaya (1948) found four definite and 29 doubtful rectal infections in 120 females

with gonorrhœa, and Wilkinson (1949) found gonococci in 18 per cent of 226 rectal smears, as against 79 2 per cent of cervical, and 61 4 per cent of urethral smears A case of rectal gonorrhœa in the male was described by Greene and Breazeale (1950)

Four cases of gonorrhœa of the median raphe of the scrotum, occurring in tubular epithelial lined tracts, were seen by Mee (1949), while Rajam and Rao (1949) reported another such case A case of gonorrhœa in a man with complete epispadias was recorded by Guldner (1950) Scott and Thomsen (1950) described three patients with cutaneous abscesses due to the gonococcus and considered that more cases would be discovered if such lesions situated near the genitals were microscopically examined more often Marmell (1952) also reported one case of gonococcal abscess of the glans penis, although this could have arisen in an aberrant para-urethral duct A case of gonorrhœal septicæmia was reported by Hirsh and Kurland (1951)

Employing the picturesque phrase 'gonorrhœal repeaters' Bundeson *et al* (1949) studied patients acquiring repeated infections, and, as might be anticipated, found that their intelligence was subnormal

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904

(2) Cultural

Gonococcal cultures were considered by Saint-Martin (1949), Moffet *et al* (1948) Le Minor (1948), Le Minor and Le Minor (1948) and Lagergren and Ouchterlony (1948) The report of the discussion by the laboratory section of the U S Public Health Association (1947) on diagnostic procedures in gonococcal infections contains much valuable information which cannot be condensed A comparison of the results obtained by twelve standard media in the U S A was made by Carpenter *et al* (1949)

Davidson and Shepard (1948) reported the results of smear and culture tests in patients with suspected gonorrhœa Putkonen and Ebeling (1950) showed that, although gonococci were more readily found in s[illegible] taken during or just after the menstrual period, the percentage of pos[illegible]

cultures remained fairly constant throughout the whole of the menstrual cycle

McLeod (1947) pointing out the superiority of properly conducted cultures over the smear in the diagnosis of gonorrhœa, advocated the use

[illegible]

and Hullinghorst (1951) and by Wilkinson (1951) for which purpose Peizer and Steffen (1947) recommended a rectangular bottle 2½ × 2½ × 4½ in, with a screw cap, containing a layer of plasma hæmoglobin agar which was then streaked with the infected material

Johnston (1948) recommended incubation of suspected material for 24 hours on ascitic fluid tyrothricin Difco chocolate agar as a reliable method for the culture of the gonococcus Mueller and Nell (1948) found that better results were obtained if cultivation was continued for 48 hours on the routine Difco medium with Supplement A, than if readings were taken at 24 hours Vera (1948) used a simple autoclaved semi solid medium

[illegible]

gonococcus most frequently found in the genito-urinary tract They were however, usually isolated from male patients in whom the signs of urethritis were mild chronic or absent When Neisseria were found in the presence of a frankly purulent discharge they were nearly always gonococci Wilkinson (1952) attempted the full identification of Neisseria found in cultures from 1 575 patients attending a venereal diseases clinic 3 4 per cent of Neisseria found in females and 1 5 per cent of those in males, proved not to be gonococci The identification of *N sicca* and *N flava* in cultures was also considered by Johnston (1951)

Eichner and Ashe (1949) reported a case in which *Bacterium aerogenes* was mistaken for the gonococcus Patkós (1949) from Hungary, noted the recent great increase in the incidence of gonorrhœa in that country and claimed to have found a Gram positive variant of the gonococcus in some chronic cases

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(3) Other tests

The gonococcus was studied under the phase contrast microscope by Haselmann and Kappel (1949)

Cooper *et al* (1950) noted that the gonococcal complement fixation test had declined in value since the advent of penicillin, and nowadays the disease is usually cured before the reaction has time to become positive The antigen for the test was considered by Le Minor (1948)

Reyn (1949, 1949*a*) conducted factor determination and serological studies employing cross absorption tests with rabbit sera A new serum test, called the polysaccharide lysis test, was described by Thomas and Mennie (1950) Like the complement fixation test it is not positive in early gonorrhœa but it is claimed to be more specific in chronic cases

Two provocative procedures for the diagnosis and test of cure for gonorrhœa have recently been described Marzocchi (1948) used pilocarpine and ergometrine apparently with success, while Bartůněk (1949) employed injections of hyaluronidase This so-called 'spreading factor',

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C. TREATMENT OF GONORRHŒA

(1) Sulphonamides

Although the principal danger of the sulphonamides, that of crystalluria resulting from acetylation, is now a rare complication of treatment, because the necessity for a sufficient fluid intake is now properly stressed, and although Lehr (1947) showed how the risk could be even further lessened by giving a combination of different sulphonamides in one tablet, *this group of drugs is now so ineffective in gonorrhœa as to enjoy little use today* Indeed a recent assessment of the spectrum of the gonococcus by Gocke *et al* (1950) showed that penicillin, aureomycin, terramycin, chloramphenicol, streptomycin, bacitracin, neomycin, polymyxin and aerosporon were all more effective *in vitro* than sulphadiazine

The decline and fall of the sulphonamides for the treatment of gonorrhœa began in Italy during World War II, and by the time penicillin providentially arrived on the scene in 1943, failure rates of up to 75 per cent were being recorded (Campbell, 1944) At this time, however, their efficiency in London remained at the 70–80 per cent level, which was surprising in view of the considerable amount of drug-fast gonorrhœa in circulation in the city However, Dunlop (1949) later had no less than 176 failures in 205 cases followed up after the administration of 25–40 g of sulphathiazole over ten days

Of the failures to sulphonamides, approximately one half fail to respond from the outset, and one half relapse after a few days Thus if one case [illegible]

of syphilis whereas all of the established antibiotics have to a greater or lesser degree Thus the use of sulphonamides is still justified as a temporary expedient in patients with gonorrhœa plus penile sores which are undergoing repeated dark field examinations to exclude syphilis Should the drug prove ineffective for the gonorrhœa, and in any event when the dark field examinations have been concluded, and the patient has been placed on serological surveillance once a month for three months, streptomycin may then be given

If syphilis is confirmed the dose of penicillin then prescribed will be *more than sufficient to cure the gonorrhœa*

For a time following the introduction of penicillin, there were isolated [illegible] show that the results obtained with penicillin plus the sul-

phonamides were superior to those achieved by either drug alone (e g

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(2) Penicillin

(a) Penicillin fractions

of gonococci, found penicillin X 13 times, F 3 3 times and K 1 5 times

entirely effective against gonorrhœa and neither penicillin X, nor any other

were sensitive to penicillin in

It was also at one time postulated that the impurities present in the

formance of crystalline penicillin G

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(b) Aqueous penicillin

When penicillin was first used for the treatment of gonorrhœa 4–6 doses of an aqueous solution were given every 2–4 hours This necessitated either admission of the patient to hospital or repeated visits by him. As soon as

delayed absorption repository penicillins became available the aqueous solution fell into disuse However, gonorrhœa may be cured with aqueous penicillins provided that a sufficient dosage is given to maintain an effective serum concentration for 8–12 hours

Heller (1946) in 396 patients reported 84–96 per cent of cures with aqueous penicillin in doses of 200,000-300,000 units given in multiple 2–3 hourly injections, while Lakaye (1946) had 94 per cent of cures in 1,374 women treated on a 12-hour regime Fawkes (1949) found that 92 7 per cent of cures in 383 patients were obtained with only 100,000 units

Inferior results, however, were reported by Mascall (1946) who claimed 18 actual and 16 probable failures in 39 patients, 5 out of 12 failures occurring after 2 4 mega units had been given for co-existing syphilis

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(c) Penicillin in oil-beeswax

In its time a most successful preparation was penicillin in oil beeswax (P O B) which was evolved by Romansky and Rittman (1945) This consisted of 300,000 units of high potency calcium penicillin per 1 c c of arachis oil with 4 8 per cent of sun bleached beeswax After 1 c c had been injected intramuscularly detectable penicillin blood levels were obtained for about 18 hours It had the disadvantage of being relatively difficult to give, owing to its viscous nature, and required a dry syringe and warming before use It has now been superseded by procaine penicillin

Heller (1946) reported 92 per cent success in 1,069 patients given single intramuscular injections of P O B Frost *et al* (1947) used subcutaneous injections in 200 cases, obtaining cures in 177 Ten per cent, however, developed local indurations and this route was not recommended Likewise Hirschberg (1948), giving single injections of only 150 000 units to 54 female prostitute prisoners, for whom default was impossible, had only two failures Eames and McClay (1948) also had 87 per cent success in 68 soldiers treated with single injections of 250,000 units Nine per cent of definite failures and 9 per cent of possible failures were, however, noted in 133 women treated by Fraser and Lome (1947)

The results obtained by P O B were summarized by Eisenberg and Laughlin (1948), who applied a sampling method in the analysis of 33,378 cases of gonorrhœa treated with 200,000 units of P O B in Chicago They estimated that the failure rate did not exceed 2 8 per cent

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(d) Procaine penicillin

When it was discovered that procaine would combine with penicillin in equimolecular amounts to form a crystalline substance, a further advance in delayed absorption preparations was made The procaine salt by itself produces more prolonged penicillin serum levels than penicillin in oil-beeswax, and procaine penicillin is quite fluid and easy to administer Suspended in arachis oil and gelled with 2 per cent aluminium monostearate, it yields even more prolonged levels After single injections of 300,000 units of the latter (P A.M), penicillin may be found in the serum for at least 24–72 hours Thus single doses of 150,000–300,000 units are all that is necessary to cure *gonorrhœa*, as a serum concentration for 12 ho[illegible]

Tucker and Hoekenga (1948) tried varying amounts of procaine penicillin G on 55 *patients with gonorrhœa* and assessed the curative dose as low as 500 units per kg of body weight Hogan *et al* (1950) likewise employed varied doses on male patients with gonorrhœa Slightly less than 10 per cent were *cured with 100* units per kg, but 92 6 per cent responded to 1,000 units per kg If the preparation was administered without regard to weight, a dose of not less than 100,000 units was recommended

Sullivan *et al* (1948), found assayable blood levels in all of 13 subjects 24 hours after receiving single injections of 300,000 units of procaine penicillin Jones and Shooter (1948), by giving such doses once daily to 45 patients were able to maintain penicillin constantly in the blood Hewitt *et al* (1948) employing single injections of 600,000 assayable blood levels [illegible]
cent at 48 hours Late[illegible]

or without aluminium monostearate, composed of particles of small size gives better results than such penicillin with particles of large size

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(e) Diamine penicillin

A new and greatly improved repository penicillin has been developed in the United States It is N, N'-Dibenzylethylenediamine dipenicillin G (Bicillin, Wyeth) It is issued in cartridges of 600,000 units of the aqueous suspension which may be fitted to a metal Tubex syringe After one such injection detectable serum levels of penicillin may persist for two weeks or more (O Brien and Smith, 1952)

In preliminary trials in gonorrhœa there were no known failures in 1,028 patients given a single dose of 300,000–2 5 million units

This penicillin was developed for the prophylaxis and treatment of infections incident to rheumatic fever and is likely ultimately to replace procaine penicillin in venereology

(f) Penicillin: *other methods of delaying absorption*

Using single intramuscular injections of 300,000 units of penicillin in a mixture of arachis oil and cholesterol, Aarseth and Sandberg (1946) obtained 41 cures in 49 cases Salminen (1949) claimed 95 4 per cent of cures of 1,840 patients given two injections of penicillin in glycerin, while Jacoby *et al* (1948) reported that 80 per cent of 1,326 men, and 87 per cent of 484 women, were cured by single injections of 200,000 units of penicillin in a water-oil emulsion

Ercoli *et al* (1948) obtained prolonged levels by mixing penicillin with adrenaline Doewe *et al* (1948) cured 123 out of 128 patients with single injections of penicillin G with ephedrine, adrenaline and a cinchona preparation, while Cohn and Kornblith (1948) cured all but three of 99 patients with a single injection of 150,000 units of penicillin in oil with adrenaline

Dowdeswell and Henfrey (1947) reported favourable results with 100,000 units of penicillin in 1½ c c of 1 per cent Planocaine, together with one third of its volume of the blood of the patient, given subcutaneously A forerunner of procaine penicillin?

All of these methods, as also the more experimental procedures such as applying ice to the injection site, have now been outmoded by the use of procaine penicillin

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(g) Penicillin: methods of delaying excretion

In attempts to produce more prolonged serum levels of penicillin after a single injection, some workers concentrated on delaying the excretion of penicillin rather than its absorption Success was finally obtained with caronamide, but, by this time, the delayed absorption methods employing penicillin in oil-beeswax, and later procaine penicillin, had already been established as simple, effective, and, above all, safe procedures Delayed excretion methods, therefore, have never been widely adopted

Merren *et al* (1948) showed that, whereas only 32 of 50 gonorrhœal [illegible]

could be prolonged by from two to sevenfold by the simultaneous use of this substance, 2 g being given every 4–6 hours (See also Sweet *et al*, 1948)

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(h) Penicillin administered by oral and other methods

At one time it was considered that some three to six times the dose of penicillin given parenterally was required to cure gonorrhœa when the drug was administered orally This has since proved to be an over-estimate as a fair percentage of cures can be obtained with smaller doses. Calcium penicillin is generally employed for oral use and the tablets are usually buffered, although the necessity for this is also not as great as was at one time thought

Ross *et al* (1947) cured 57 out of 63 adults by giving 50,000 units of penicillin orally every 3 hours for six doses, and 28 out of 33 children with 200,000–300,000 units Bushby and Harkness (1946) gave six doses of only 40,000 units at 3-hourly intervals to 62 patients, prescribing

potassium citrate in addition and restricting the fluid intake to 1½ pints The majority of these patients were followed up for six months and only two failures and one case of epididymitis were noted Porudominskii and Zalutskii (1948) treated 97 cases, of which 73 had sulphonamide-resistant gonorrhœa, with 200,000–300,000 units of penicillin given orally, and claimed 79 cures

Previously Seager *et al* (1946) successfully treated 15 cases orally in- [illegible] and 46 cures out of 50 when 900,000 units were given over 7 hours

More recently Robinson (1950) obtained 80 0–86 7 per cent of cures in 70 of 98 males who were given only 250,000 and 500,000 units of penicillin in buffered tablets Jacoby and Ollswang (1950) treated 284 males and 25 females with oral doses of 400,000–600,000 units and obtained 82–84 per cent of cures in males, and 72–100 per cent in females In Great Britain, Horne (1950) treated 50 male patients with 500,000 units of calcium penicillin orally, repeating the dose 3–6 hours later There were only three failures, one of which was suspected of being a reinfection Johnson *et al* (1951) employed a buffered oral mixture of penicillin and sulphonamides

Absorption rates of penicillin from the stomach, and the serum levels obtained, vary from individual to individual This fact, coupled with the memory of the dissemination of drug fast strains of gonococci which followed the widespread use and abuse of the sulphonamides, and doubtless also the fear that patients might resort to self-medication, has resulted in some disfavour of the oral route However, occasionally patients are 'allergic' to needle puncture or the physician may have to prescribe in the absence of equipment (e g during air travel, etc), and on these occasions oral penicillin, as the other oral antibiotics, has a definite place

Taplin and Thompson (1948), noting that penicillin blood levels could be sustained for 24 hours following the *inhalation* of penicillin glucose and penicillin plasma mixtures, treated 25 patients with either 50,000 units inhaled every 3 hours, or with single inhalations of 150,000–300,000 units There were only four failures attributable to the method

Goldberger *et al* (1947) reported that assayable blood levels were obtained three hours after the insertion of a *vaginal suppository* of penicillin and suggested further trials

The French adapted the new antibiotic drug to ancient techniques and Debray (1949) reported on the results obtained by *submucous injections* of penicillin into the cervix and around the urethra

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R,

(i) Penicillin failures

Although penicillin was first used in the treatment of gonorrhœa during 1943, it continues to give excellent results and no evidence of any widespread resistance of the gonococcus has so far been encountered Many of the local findings to this effect were reported from the Mediterranean seaboard and more distant parts of the world where the possibility that the penicillin had deteriorated in transit, or had been tampered with, could not be entirely excluded

Penicillin-fast strains of gonococci can, however, be produced in the laboratory Bahn *et al* (1945) and Mills (1949) discussed the penicillin-resistant gonococcus If a situation was going to develop with penicillin such as occurred with the sulphonamides it should be evident by now, although Gocke *et al* (1950), testing the gonococcus *in vitro*, suggested that there might have been some deterioration in its sensitivity to penicillin between the years 1947 and 1949 Variations in penicillin sensitivity in 66 so-called 'penicillin failures' were reported by Cohn *et al* (1949)

A less cheerful picture was drawn by Mascall (1947) who claimed 18 actual and 16 probable failures in 39 patients treated, 5 out of 12 failing when no less than

From the same cl

of 1,788 male and

with 150,000 units of penicillin alone given in five equal doses at 2-hourly intervals They reported an unsatisfactory treatment rate of 34 5–44 2 per cent in males and 16 4 per cent in females. However, on critical analysis

lesser figure included the reinfections, and in any event a relatively small

evacuated from the Pacific theatre on account of so-called 'drug-fast

urethritis Some clinical cases of penicillin-fast gonorrhœa were, however, reported by Chen *et al* (1949) but these were readily cured by aureomycin

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has always been kept in mind, and clinics in Great Britain have generally observed cases of gonorrhœa treated with penicillin for a period of six months It must, however, be admitted that cases of syphilis showing themselves after the third month are extremely rare Indeed, the incidence of

evidence to show that simultaneously acquired syphilis was being cured in the incubation period

In the U S A Moore (1947) considered that four months was an adequate time for syphilis to show itself after the treatment of gonorrhœa with penicillin, but some American clinics have taken the realistic view that the duty of the physician when a patient attends with gonorrhœa

ate later

patients

to this

ing of

urethral and prostatic smears and cultures once a week for three weeks In New York, Jacoby and Rosenthal (1950) have now questioned whether even this short period is not excessive In view of the large numbers of

re the second and third attendances, and the small numbers

of failures noted at these later visits, they recommended as a practical measure that only *one* post-treatment check at one week should be made

Cronin (1947), in a critical review of published cases, stated that there was no evidence that penicillin in doses up to 150,000 units delays the onset of syphilis beyond three months MacFarlane (1950), from Newcastle, England, [illegible]

[illegible]

relationship

Many patients incubating syphilis during treatment with penicillin for gonorrhœa have a febrile Herxheimer reaction Symptoms resembling influenza, immediately following treatment with penicillin, therefore, should stimulate the physician's awareness of the possibility Fromer *et al* (1946) found that of 1,000 cases of early syphilis 66 had previously received penicillin for gonorrhœa and on close questioning 18 of these gave a history of symptoms suggestive of a Herxheimer reaction at the time that the penicillin was given Reekie (1951) reported three cases of this phenomenon

The problem of masked syphilis has probably been exaggerated Certainly a later follow-up of discharged American military personnel, who had been treated with penicillin for gonorrhœa in the [illegible]

[illegible]

than reduce it to its lowest effective limit, so as to make the possibility of cure more likely A case can therefore be made out against giving only 150,000 units of procaine penicillin, in favour of twice the amount, or more The same effect will be achieved by the use of the diamine penicillin, Bicillin

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[illegible]

(3) Streptomycin

Streptomycin in single doses is also effective in the treatment of gonorrhœa The injection causes slightly more discomfort than penicillin but, in the small doses used, there are no dangers of toxic complications apart from occasional sensitization dermatitis in the operator or patient

Pulaski (1947) obtained cures on a small number of cases, and Chinn *et al* (1947) claimed no less than 70 out of 72 cured with 0 2–0 5 g of this drug [illegible] –0 6 g where [illegible] t there were [illegible] *et al* (1950) had 17 cures in 18 women treated, while Taggart *et al* (1950), using the newer dihydrostreptomycin, cured 95 of 104 with single injections of 0 2–0 4 g Jacoby *et al* (1950) had 57 cures in 66 given 0 5 g and 69 out of 73 receiving 1 g Some resistance to the drug was noted in the failures

Putkonen and Rouhunkoski (1951) also used dihydrostreptomycin Of 24 women receiving 0 1 g 16 were cured, while 23 out of 30 were cured with 0 2 g and 86 of 89 with 0 4 g In a control group 65 out of 66 were cured with a single injection of 150,000 units of P A M

Willcox (1951) treated 17 patients with single injections of 0 2–0 6 g of streptomycin with complete success in 11 Two later developed non-specific infections, two had reinfections and there were two proved failures Of 35 receiving 1 0 g there were 22 complete successes, six with non specific infections, four with reinfections and three failures

Organisms readily become resistant to streptomycin and, if no scientific investigation is being made on the patients (in which case the rule should always be to retreat the failures first with the same drug), it is better to retreat when necessary with a different antibiotic Should streptomycin be widely used for gonorrhœa it is possible, therefore, that its efficiency may decline

Fisken and Gruhzit (1946) showed streptomycin to be relatively inefficient against syphilis Willcox (1948) found *T pallidum* without difficulty [illegible]

for a maximum of three months It is therefore indicated in all cases of gonorrhœa in which the possibilities of concomitant syphilis are above [illegible]

[illegible]

pected to be false positives, and patients with a history of intercourse with [illegible]

[illegible]

as they often will, then 0 5 g of streptomycin may be used.

Streptomycin may also be given by the 'Hypospray'—a form of jet injection (Hirsh *et al* (1948))

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(4) Aureomycin

Collins *et al* (1948), and Finland *et al* (1948), reported that gonorrhœa could be cured with aureomycin which is given orally Of 69 cases treated with an average of 1 3 g over a period of 1 2 days, 49 were cured, one was considered a dubious success, and six were failures Willcox and Findlay (1949) had success in two cases given 1 0 and 2 0 g respectively in divided doses In a later report Collins *et al* (1949) had 87 per cent of successes in 122 patients given 1 0–3 5 g orally over 12–36 hours *In vitro* they found it superior in action against the gonococcus to streptomycin, bacitracin, polymyxin and sulphadiazine but not to penicillin

Robinson (1950, 1950*a*) obtained 36 cures in 70 patients given single doses of 1 0 g of aureomycin orally In 3 out of 7 treatment failed when only half that dose was given Later, Robinson and Galen (1951) reported a 79 per cent cure rate in 120 patients treated with single doses of 1 0–2 0 g This was not as high as the 95 per cent cure rate obtained in a

c

control series treated with single injections of P A M Using a more prolonged dosage, Chen *et al* (1949) cured all of 20 cases of gonorrhœa, including some showing resistance to penicillin, by means of 1 0 g given three times a day for 2 days Such doses, however, might conceal an incubating syphilitic infection—for aureomycin, chloramphenicol and terramycin are all active in that disorder

Wright *et al* (1951) treated 63 patients with two doses each of 1 0 g given 6 hours apart, with three failures Three capsules each of aureomycin and chloramphenicol were used together on 19 patients by Chen *et al* (1951)

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(5) Chloramphenicol

Greaves *et al* (1950) had 48 cures in 50 patients given a single oral dose of 750 mg of chloramphenicol, 12 in 16 given a single dose of 500 mg, and only one in four given 250 mg Single doses of 1 0–3 5 g were given to 48 others by Smadel *et al* (1949) and, although there were 10 relapses during the one month of surveillance, these responded to retreatment with 3 g Using a more prolonged dosage Chen *et al* (1949) cured 13 of 14 with 6 g given over a period of 2 days, but only 7 of 10 given 3 g responded Robinson and Robinson (1949) treated seven cases with an initial dose of 2 g followed by 1 g at intervals of 4 hours In five cases the discharge stopped at once and in the remaining two after a further 3 g had been given Six others receiving a single oral dose of 3 g, followed in three by two doses of 1 g at intervals of 4 hours, were also cured Willcox (1949) also reported success with two patients

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(6) Terramycin

Robinson (1950) had three failures in six patients given a single oral dose

Seven patients were treated by Caldwell *et al* (1950), and one patient was treated successfully with 2 0 g over two days by Sayer *et al* (1951) Wright *et al* (1951) treated 177 patients on a number of schedules A cure rate of 88 7 per cent was obtained on 120 patients given two doses of 0 5 g at an interval of 6 hours Putkonen (1951) treated 67 women with
confined observation for
re cured, and of 55 given

Of 26 others given a single dose of 1 0 g by Schoch and Alexander (1950) 24 had negative smears one day later Willcox (1951) also reported 30 cases Of six receiving single doses of 1 0–2 0 g there were three failures, while of 19 given two doses of 1 0 g at an interval of 6 hours there were two relapses, two with non specific infections and one reinfection In a later paper Willcox (1952) reported 44 patients treated with 2 g of terramycin in eight doses over 48 hours Of 38 followed up there were four reinfections, four non specific infections and three (8 per cent) definite failures

Beinfield *et al* (1951) attempted a comparison between terramycin and aureomycin in doses of 1 0–2 0 g given over 24 hours Of 130 treated with terramycin 106 were followed up and there were five relapses Of 130 treated with aureomycin 107 were followed up and there were four relapses The use of the newer antibiotics in the treatment of venereal diseases generally was considered by Robinson (1952)

References

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Ass , 143, 4–5
Putkonen -18
Robinso
Robinso
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459–60

nell, M

D. COMPLICATIONS OF GONORRHŒA

(I) Arthritis

The complications of gonorrhœa are of increasing rarity Amongst U S troops in World War I, gonococcal arthritis was noted in no less than 3 per cent of those afflicted with the disease In World War II, however, the figure declined to 0 2–0 3 per cent At the Belle Vue Hospital, New York, Bunim (1948) reported that there were 49 cases in the first 45 months *of sulphonamide therapy, but during the first 45 months after the intro*duction of penicillin the figure had decreased to 10

Prior to and during the sulphonamide era the value of fever in the treatment of gonococcal arthritis was well known Indeed Veermeer (1948) noted that fever given concurrently with the sulphonamides appeared to enhance the defence mechanisms, notably the leucocyte count and the opsonic index Likewise Hagerman (1950) showed that 12 out of 14 strains of gonococci were more susceptible to penicillin when incubated at a higher temperature Hagermann *et al* (1952) reported 30 cases treated

many cases diagnosed as gonococcal arthritis are in reality cases of Reiter's syndrome occurring in gonorrhœal patients

Spitzer and Steinbrocker (1949) treated 28 cases of gonococcal arthritis with 0 5 7 0 mega units of penicillin given over a period of 3–30 days Bacterial cure of the extra-articular focus was obtained in all, but the arthritis was not improved in five, although it was greatly improved in 15 and cured in eight Robinson *et al* (1949) considered 202 patients with gonorrhœal arthritis treated with penicillin, sulphonamides and fever Malhotra (1950) reported 46 smear-positive cases of gonococcal arthritis and suggested that a preliminary course of streptomycin might replace fever therapy Hirsh and Kurland (1950) successfully treated three such *cases with 0 5 g of streptomycin every 4 hours for 6–10 days*

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(2) Other complications in adults

A case of gonococcal *endocarditis*, successfully treated with 23 mega units of penicillin and 62 g of sulphadiazine over 31 days, was reported by Dorset *et al* (1949) That the heart may be affected subclinically in com- [illegible]

[illegible] years previously

Hundley *et al* (1950), after an attempt to ascertain whether the recurrences of *acute salpingitis* arose from dormant foci in the fallopian tubes, or from reinfection from below, considered the latter to be the case Falk (1951) discussed the surgical operation of cornual resection in chronic salpingitis The treatment of *Bartholin's cyst* by marsupialization was discussed by Jacobson (1950), and the minor surgical procedures in vogue in France were described by Durel (1951)

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(3) Vulvo-vaginitis

Mukherjee (1950) studied 240 cases of vulvo-vaginitis in children Gonococcal infections accounted for 54 5 per cent and non-specific infections for 35 6 per cent Weaver (1950) reported that, of 1,014 children examined in a State School in Texas, inflammatory genital changes were found in 262 Four had gonorrhœa and 12 a vaginitis in which the Neisseria found were later identified as *N sicca*

Clarke and Eisenberg (1947) [illegible]
va [illegible]
ce [illegible]

for although most patients respond in the first instance a number relapse Many of these cases show Neisseria in the smears but these are not always confirmed by culture, and it may well be that they are Neisseria other than the gonococcus Reynes (1947), for example, isolated from a five-year-old child a new species of Neisseria which digests milk and liquefies gelatin, which he named *N vulvo vaginitis*

References

[illegible] 707–10
[illegible]

(4) Ophthalmia Neonatorum

In rabbits the possibility of ophthalmia developing after the introduction of gonococci into the anterior chamber of the eye depends to a large extent on the size of the inoculum Miller (1948) found that if 20 million organisms were introduced, ophthalmia was produced in 93 per cent of rabbits If only two million were introduced, however, the percentage of 'takes' was reduced to 45 per cent Penicillin, sulphathiazole and calomel, introduced soon after inoculation in a watery or vanishing-cream base, but not in an oily medium, were all found to be satisfactory prophylactic agents

Although the sulphonamides (as sulphacetamide) are sometimes used (Bickel, 1950), penicillin is undoubtedly the drug of choice in the treatment of gonococcal ophthalmia, although silver nitrate has not yet been superseded in its prophylaxis This view was held by Benedict (1950) Sorsby (1949) reported 400 cases of ophthalmia neonatorum The same author (1950) described his technique of local treatment with penicillin and recommended that ocular drops be used containing 10,000 units per ml, which should be instilled every minute for 30 minutes followed by six instillations at 5 minute intervals, and six each at half hourly, hourly and 2-hourly intervals, for a total of 22 hours of treatment The results were excellent and he considered that properly treated the condition need no longer cause blindness He also advanced the view that its eradication lies not in finding an alternative prophylactic drug to silver nitrate but rather in curing the maternal infection This could be achieved by the routine treatment of the mother during the last week of pregnancy with a single injection of penicillin, but it is a method of prevention which has not yet been exploited

Franklin (1948, 1948*a*), on the other hand, affirmed that local penicillin drops were superior to silver nitrate and also less irritating Allen and Barrere (1949) considered certain aspects of ophthalmia but their data were insufficient to compare the prophylactic merits of silver nitrate and penicillin Watts and Gleich (1950) report that of 4,565 infants born at the

Harlem Hospital, New York, during the year ending June, 1949, and given both penicillin *and* silver nitrate locally, not a single case of gonococcal ophthalmia was observed

no case of ophthalmia was observed

Clark and Culler (1951), and Culler and Clark (1951), used a single prophylactic instillation of aureomycin, apparently with success

References

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E. PROPHYLAXIS OF GONORRHŒA (see p 189)

Before the introduction of the antibiotics, sulphonamides given orally proved efficient prophylactics against both gonorrhœa and chancroid

failures were reported in 10,000 men

Sulphonamides might be expected to prevent gonorrhœa, chancroid and lymphogranuloma venereum but they have no action upon syphilis, non specific urethritis and granuloma inguinale In any event their efficacy against gonorrhœa has now deteriorated, and more recent work has been with the antibiotics

Eagle *et al* (1948, 1949) reported success with oral penicillin U S naval personnel were divided into two groups half acted as controls, and the other half received oral penicillin immediately after returning from a

for although most patients respond in the first instance a number relapse Many of these cases show Neisseria in the smears but these are not always confirmed by culture, and it may well be that they are Neisseria other than the gonococcus Reynes (1947), for example, isolated from a five-year-old child a new species of Neisseria which digests milk and liquefies gelatin, which he named *N vulvo-vaginitis*

References

[illegible] 707-10

[illegible]

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CHAPTER II

GRANULOMA INGUINALE

A. CLINICAL

MARMELL and Santora (1950) discussed the nomenclature of granuloma [illegible] *Donovanosis* be applied to this [illegible] cases from Trinidad were des- [illegible] es seen in Southern Rhodesia were reported by Willcox (1951), and the first case to be seen on the island of Java by Van der Meulen (1950) Cutler *et al* (1952) presented illustrative case histories of six patients seen in the Himachal Pradesh, India Only one male and one female case were reported from the clinics of England and Wales in 1951

Packer *et al* (1948) reported a case of granuloma inguinale of the cervix and vagina with bone metastases, and another case with metastatic spread to the bones was described by Lipp and Bibby (1950), while Eisenberg (1948) noted one with oral lesions Of 190 cases seen in six years by Hanna and Pratt Thomas (1948) there were six in which, in addition to genital lesions, other parts were affected In five the lips were involved, with neck and face in addition in three, and in one the cheek and neck Three cases of granuloma inguinale of the cervix were reported by Hoge and Salzberg (1950) A fatal case was reported by Rhinehart and Bauer (1947) in which, [illegible]

Although the disease can be cured by the antibiotics, surgery is sometimes necessary to correct distortion resulting from scarring Pettit and Thomas (1950) described four cases in females in which vulvectomy had to be performed

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[illegible]

Pett[illegible] M D, and Thomas, C C (1950) [illegible] 261–4

B EXPERIMENTAL

Dienst *et al* (1947) successfully passed the responsible organism, *Dono-*

reaction, in which lipoid droplets but no Donovania were seen, was produced when an egg yolk culture was inoculated into the eye of a rabbit No such reaction was noted in control eyes inoculated with uninfected egg yolk

Thomison (1951) inoculated contaminated material containing *Dono-* hatched chicks The con- ata containing Donovania

Chen *et al* (1951) tested the bacteriostatic and bactericidal powers of antibiotics dihydro bacitracin This is curious in view of the *ineffectiveness of penicillin in the clinical infection*

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C. DIAGNOSTIC

(1) Tissue smears

The technique of tissue spread for the demonstration of Donovania was described by Cannefax (1948), and a simple stain for Donovania employing a pinacyanole dye, by Greenblatt *et al* (1951)

References

Cannefax G R (1948) *J vener Dis Inform* **29**, 201–4
Greenblatt, R B, Dienst, R B, and West R M (1951), *Amer J Syph*, **35**, 1–3

(2) Skin tests

Dienst *et al* (1949) employed chick embryo cultures as an antigen for a

have also been considered by Packer and Dulaney (1949)

References

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Packer, H, and Dulaney, A D (1949), *Amer J Syph*, 33, 68 75

(3) Complement fixation tests

Dunham and Rake (1948) showed that *Donovania granulomatis* can be grown on artificial media An antigen was prepared from a subculture which

granul

lymph

varicose ulcer, but in none of 10 with tuberculosis or in four normal persons

Dulaney and Packer (1947) had previously obtained an antigen for the complement fixation test from an abscess on the back of the hand of a

y obtained 21 positive reactions in

plete duplication of the results of the complement fixation test performed with an antigen of *Donovania granulomatis* when the antigen was prepared from cultures of Friedlander's

antigen prepared from granuloma inguinale material

References

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Dunham

Pack –95

Pack

Rake

D. THERAPEUTIC

(1) Antimonials

Although the best drugs of their time, and reasonably effective if prolonged *treatment was used, the antimonials were frequently attended by resistance* and relapses The antibiotics have since proved superior, less toxic, and more rapid in their effects

Of 97 cases observed by Marshak *et al* (1948), 25 received daily injections of one per cent potassium antimony tartrate, commencing with 1 c c and increasing by that amount daily to a maximum of 10 c c, and then decreasing at the same rate until a total of 100 c c had been given The lesions of 21 of these had healed by the end of the course, two required a second course, and two did not respond Allison (1948) observed apparent cure in 60 per cent of 65 Negroes treated with 5–42 (average 20) injections of Anthiomaline The results were considered comparable to those obtained with other tried antimonials

Thomas (1951) in a review of 79 cases considered that the antimonials should be entirely replaced by antibiotics

References

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T J (1948), *Arch Derm Syph*
nec, 61, 790–800

(2) Streptomycin

Rake and Dunham (1947) tested penicillin, streptomycin, the toxic streptothricin, and other chemotherapeutic agents including the antimonials and the sulphonamides, as to their power of protecting embryonated chicks when mixed with an inoculum containing Donovania Tartar emetic, streptomycin and streptothricin were all successful Clinically Greenblatt *et al* (1950) reported that penicillin, tyrothricin and bacitracin were ineffective but that streptomycin, chloramphenicol, aureomycin and terramycin were effective

Greenblatt *et al* (1947, 1947*a*) found that a total dose of 20 g of streptomycin given intramuscularly over five days was an extremely effective course By the time that 59 patients had been treated with streptomycin on varied schedules and observed for up to eight post treatment months, only four failures had been observed This series was raised to 91 by Kupperman *et al* (1948) and to 100 by Chen *et al* (1948) In the 54 cases given 20 g over five days there were no initial failures and only four la [illegible] (1950) ... ed the ser es still further to 14
[illegible] red

d resistant Portions of
' (1949) and Wammock
76 treated with strepto-
mycin 61 responded to one course and only three cases proved resistant

Other workers reporting successful results with streptomycin include Marshak and Rodriquez (1948)—11 cases, Hirsh and Taggart (1948)—21 cases, Barton *et al* (1947)—3 cases, Zimmerman and Smith (1948)—85 cases, Thompson *et al* (1948)—3 cases, Mason and Welsh (1948)—4 cases, Stewart and Laur (1949)—6 cases; Samitz *et al.* (1949)—19 cases; Freed and Kern (1950)—6 cases; and Hoge and Salzberg (1950, 1950*a*)—8 cases Willcox (1950) observed 17 cases in Southern Rhodesia and seven out of eight treated with streptomycin responded Jacoby *et al* (1949) reported 37 cases treated on an ambulatory basis

Dienst *et al* (1950) implanted a piece of granulation tissue from a streptomycin-resistant case into a
tainir
resist

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261–8

Toxic effects of streptomycin

Toxic effects with streptomycin include ninth day erythema of an allergic type, cylindruria without renal involvement, and eighth nerve involvement Such are encountered with the prolonged therapy used for tuberculosis (Farrington *et al* (1947)) but are less seldom noted in the doses given for granuloma inguinale

Four cases of vestibular disturbance were noted by Nielsen and Marsh (1948), three of stomatitis by Beham and Perr (1948), one of agranulocytosis by Feld (1949), and a fatal case of encephalopathy by Hunnicutt *et al* (1948)

[illegible]
et [illegible]
Fo [illegible]
et al (1948) Patch tests with streptomycin performed on 212 persons by Goldman and Feldman (1948) were negative but were shown to be positive [illegible]

[illegible]
al (1948) that the newer dihydrostreptomycin was less toxic, although later work has not confirmed this

These considerations need cause little concern in the treatment of gonorrhœa and non specific urethritis in view of the small doses usually given They are of greater importance, however, in the treatment of soft sore, Reiter's disease and granuloma inguinale

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FIG 2—EXPERIMENTAL LESION OF GRANULOMA INGUINALE PRODUCED BY MATERIAL FROM A STREPTOMYCIN RESISTANT CASE THIS LESION WAS ALSO RESISTANT TO STREPTOMYCIN BUT RESPONDED TO AUREOMYCIN See p 29

(Dr R B Greenblatt U S A)

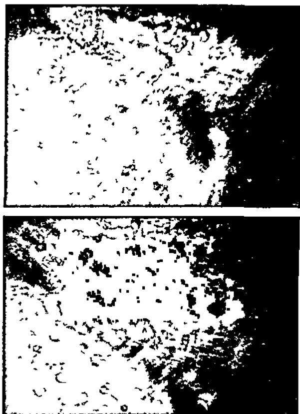


FIG 3—LESION OF A STREPTOMYCIN RESISTANT CASE OF GRANULOMA INGUINALE WHICH RESPONDED TO AUREOMYCIN
(Dr R B Greenblatt, U S A)

(3) Aureomycin

This drug is also effective for granuloma inguinale and will cure those cases which fail to respond to streptomycin (Fig 3) Greenblatt *et al* (1948) noted that three patients failed to respond to aureomycin given parenterally but did so when the drug was given orally They recommended one 250-mg oral capsule four times a day for 5 days as a suitable course, [illegible]

In a later assessment Greenblatt *et al* (1950) reported that of 46 patients treated with aureomycin in doses of 500 mg four times daily for 10–15 days (20–25 g) there were only two failures, both of which responded to a second course Nausea and vomiting, however, occasionally proved tiresome More prolonged treatment was given to patients with extensive lesions In a later paper still (Greenblatt *et al* (1952)) 71 cases were reported. Among 66 followed up there were 11 recurrences

Robinson *et al* (1949), giving 20 mg intramuscularly each day for 23–31 days, found the drug less satisfactory than streptomycin in six cases Oral doses of 4 2–40 g produced an initial satisfactory response in 27 of 36 cases No untoward effects were noted Robinson and Cronk (1951) made a further assessment after 42 cases had been treated There were 12 relapses in 19 patients given 9 g or less, and 10 relapses in 23 receiving 20–40 g chloramphenicol was preferred

[illegible]

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(4) Chloramphenicol

Greenblatt *et al* (1950) employed chloramphenicol in the same doses as aureomycin (20 g in 10 days), but increased the dose to 50–70 g in the

presence of extensive lesions or slow healing. Employed on 23 out-patients it regularly caused rapid healing and there were only two relapses, both of which responded to retreatment. The drug was preferred to aureomycin, as it appeared to be less toxic. In a later paper Greenblatt *et al* (1952) reported 46 patients treated and there were 10 recurrences of which nine responded to retreatment with chloramphenicol

Nine patients were given 500 mg of chloramphenicol four times daily for 12½ days by Zises and Smith (1951) There were no relapses during a follow-up of 2½–12 months Robinson and Cronk (1951) gave 20–40 g to 16 patients and there were four relapses The drug was, however, preferred to aureomycin

Harb *et al* (1951) used a suspension of chloramphenicol in saline and, after 4 g (8 ml) had been injected intramuscularly, it was claimed that a detectable serum level of the antibiotic could be maintained for 72–96 hours Forty-three cases of granuloma inguinale were treated with 6 g given in three injections over 8 days, and 38 responded satisfactorily

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(5) Terramycin

Hendricks *et al* (1950) reported satisfactory healing of the lesions of two patients with granuloma inguinale who were given 60 mg/kg of terramycin daily for 12 days The Donovan bodies disappeared by the third day

Whitaker *et al* (1951) treated five cases with 12–32 g and all responded well, and 11 others successfully treated were reported by Wright *et al* (1951) Niedelman *et al* (1951) considered 4 g daily for 10–20 days to be a satisfactory course and had good results in five of six cases so treated

Greenblatt *et al* (1951), on an experience of 32 cases treated with terramycin, recommended 2 g daily for 12½ days In a later report (Greenblatt *et al* (1952)) the series was increased to 36 cases Of 27 followed up for 1–18 months, two patients required a second course but both of these responded the second time

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CHAPTER III

LYMPHOGRANULOMA VENEREUM

A. CLINICAL

(1) General

THERE were 66 male and 3 female cases of lymphogranuloma venereum reported from the clinics of England and Wales in 1951 General reviews of the condition were presented by Parks and Fraser (1947), and Coutts (1950) Nine Chinese cases were described by Laube (1949) Coutts (1946) reported 32 cases of genital œdema, ascribed to this disease, from Chile where filariasis is unknown (Fig 4)

A case of lymphogranuloma venereum in a Negro girl aged sixteen months was reported by Thompson and Higgins (1949) Five cases associated with intense vascularization of the cornea and a poor prognosis for vision were reported by Scheie *et al* (1947), a case presenting as a pyrexia of unknown origin was recorded by Luger (1948), and one with an arthritis of the hip joint by Sampaio and Farrajota (1950)

A case of chronic adhesive arachnoiditis, thought to be due to lymphogranuloma venereum, was reported by Valergakis *et al* (1949) The cerebrospinal fluids of 82 patients were tested by Finberg *et al* (1949) who found abnormalities in 19 These usually took the form of a raised protein content or an abnormal mastic test The spinal fluid of 25 others, however, was examined by Leifer (1947) who found no such abnormalities in any, and no false positive Wassermann reactions

A case of pericarditis with enlarged mediastinal and supraclavicular glands, the virus being recovered from the latter, was reported by Sheldon *et al* (1948)

Pund and Lacy (1951) after Frei-testing a number of patients with carcinoma of the external genitalia considered that lymphogranuloma venereum was one of many predisposing causes

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(2) Female

Owing to the different arrangement of the lymphatic drainage in the female the disease is more serious in that sex, and peri proctitis, proctitis and rectal strictures are common The use of an aero-rectogram to determine the site of the stricture was advocated by Jones (1949) A case of intestinal stricture 12 cm from the anus in an Argentinian, which was successfully treated with intravenous 'Lygranum', was reported by Solari (1949)

Jaffe (1948) reported that 65 of the deaths in 96 cases of lymphogranuloma venereum discovered in 5,900 autopsies were directly or indirectly due to proctitis Surgical excision of the affected rectal and colonic areas was performed by Adams *et al* (1948) with a mortality of 8 1 per cent in 62 cases

In the pregnant woman difficulties at confinement may result from obstruction by vulvar esthiomene like lesions, or as a result of scarring in the soft tissues of the pelvis Although the published mortality of mothers with active pelvic lymphogranuloma venereum has been about 6 per cent, Kaiser and King (1947) reported 38 deliveries in 26 such women without any maternal deaths or exacerbation of the lesions, three Cæsarian sections were performed Steer (1947), reviewing the pregnancies of 75 affected women, considered that it is unwise to run the risk of labour if there is rectal stricture or active disease, and that termination of pregnancy should be considered If this is not possible a Cæsarian operation was advised Schiebel (1951) considered that dilatation of rectal strictures is never curative as fibrous strictures never disappear and the mucosa destroyed over large areas never regenerates Abdomino perineal resection was considered a more satisfactory procedure

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[illegible] *Obstet Gynec*, 54, 219–29
[illegible] 12, 49–52
[illegible] 404–10
[illegible], 230–4

B. PATHOLOGICAL

(1) General

found The pathology of the disease has also been considered in some detail by Sheldon and Heyman (1947) The Gamna bodies were believed to be phagocytes

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(2) Viral

Viruses and the venereal diseases were considered by Bedson (1950)

Beeson *et al* (1946) isolated the virus of lymphogranuloma venereum from the buboes of six males and one coloured female, but only in the female case could it be found in the blood and the cerebrospinal fluid although the latter was normal to routine tests Wall (1946) isolated the virus from bubo fluids, excised lymph nodes and from a penile lesion in 28 out of 33 patients diagnosed as suffering from lymphogranuloma venereum The virus was obtained in 39 out of 40 specimens by mouse brain inoculation, and in 32 out of 41 tested by a yolk sac procedure Secondary infection proved a technical difficulty of the latter method Moreover a result was obtained 5–14 days later than the 3-7 days required if mouse brain techniques were employed Transmission of the virus from man to mouse was considered by Levaditi *et al* (1949)

Heyman *et al* (1947) identified the virus in bubo pus, or in saline aspirates from lymph nodes, in untreated patients with lymphogranuloma venereum and in those treated with sulphathiazole In two out of three untreated cases the virus was still present 95 days after the onset of the disease In treated cases the virus could not usually be found after sulphathiazole had been given for two to three weeks, although it was still identified in the excised lymph node of one patient four months after receiving no less than 120 g

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C. DIAGNOSTIC

(1) Skin test

Lépine *et al.* (1948) stated that antigens prepared from the brains of infected monkeys remained effective for the Frei test when kept at room temperatures for several months. Results of the skin test performed with the yolk sac antigen 'Lygranum' were discussed by Shaffer and Rake [illegible]

[illegible]

with Lygranum antigen, was described by Floystrup *et al.* (1950). Reymann (1951) found the skin test highly specific in Denmark In Finland Sonck (1949) used the Frei test on 102 children born of mothers either with clinical lymphogranuloma venereum, or with evidence of past disease. Eighty-eight of the tests were negative and placental transmission of the disease, therefore, was considered rare Fisch (1949) found the disease [illegible]

[illegible]

also found in 110 prostitutes later at São Paulo (*J A M A* , 1951) Willcox (1949) showed by means of the Frei test that in 479 Africans of Southern Rhodesia, lymphogranuloma venereum was principally a disease of the towns (Table 2).

TABLE 2

LYMPHOGRANULOMA VENEREUM IN AFRICANS
SKIN TESTS WITH LYGRANUM IN SOUTHERN RHODESIA

	Tests	Pos	Neg	Percentage pos
V D patients (Urban)	345	48	297	13 9
Normal soldiery (Urban)	81	8	73	9 9
Hospital patients (Rural)	53	1	52	1·9
Total	479	57	422	8 8

Grace *et al* (1952) showed that positive Frei tests could be made temporarily negative during treatment with cortisone, whereas no change occurred in the complement fixation reaction

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[illegible] 74, 140–2
[illegible] 88–93
[illegible]

(2) Systemic reaction

The systemic reaction, consisting of fever occurring in patients with lymphogranuloma venereum, about 6 hours after an intravenous injection of Frei's antigen and lasting 32–52 hours, was noted by Le Coulant (1948) On the other hand, in a general review by Costello and D Avanzo (1948), who analysed some 388 case records of patients treated over a 10-year period at the Belle Vue Hospital, New York, it was noted that the systemic reaction was less reliable than the Frei test (86 per cent of positives as against 95 6 per cent)

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(3) Complement fixation test

The antigen for the complement fixation test was considered by Hilleman and Nigg (1948) and by Reyn (1951) Dulaney and Packer (1947) found that the complement fixation diagnostic test was satisfactory in dilutions of 1 40 or over, but that at lower dilutions false positive results might occur Wall *et al* (1947) studied the same test in 27 cases of lymphogranuloma venereum, and in 45 cases of chancroid In 20 of the lymphogranu-

Hospital, New

were demonstra

of 178 Negro college students and 6 of 90 white persons were positive—all at a low titre Employing the complement fixation test in Britain, Bedson *et al* (1949) found positive readings in 28 of 32 patients in whom the diagnosis of lymphogranuloma venereum was certain, in 7 of 31 in whom it was possible, and in only one of 67 in whom it was doubtful

A single positive test is believed to be insufficient evidence for the diagnosis of lymphogranuloma venereum, as it may indicate only a past infection with some member of the group A repeated test to observe a rise in titre is recommended Of 27 patients with clinical lymphogranuloma venereum tested by Wetherbee *et al* (1951) all but two gave positive titres of 1 40 or higher, while only 2 4 per cent of 249 adult controls showed positive results, and 57 children without sexual contact gave negative reactions Positives to a titre of 1 20 or higher were noted in 7 4 per cent of syphilitics but 26 per cent had titres of at least 1 5 All but two of 27

40 or greater

or higher, was

mphogranuloma

venereum group of viruses Macrae (1951) performed this test in Britain Of 70 male patients with venereal disease under investigation, mainly seamen, there were 30 positives, of 192 male blood donors there was one positive Of 150 Wassermann-negative sera from patients referred for a blood test there were 11 positives, while of 156 Wassermann positive sera there were 21 positives Of 51 sera from patients suffering from miscellaneous diseases there were no positives

Hilleman *et al* (1951) described conglutinating complement fixation, and hæmagglutination tests, and compared them with the complement fixation test, which was found to be the most satisfactory in man

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D. THERAPEUTIC

(1) Sulphonamides

Although Juguet (1949) claimed that repeated injections of non specific sera (e g anti pneumococcal, anti gas gangrene, or anti tetanus) were curative in some patients, the sulphonamides still have pride of place The prevalence of the disease in Eritrea, and its response to sulphonamides, was stressed by Maffi (1948) Willcox (1952) reported 120 cases treated by *sulphonamides in the Gold Coast*

(2) Penicillin and Streptomycin

Streptomycin has no effect upon yolk suspensions of the virus, although penicillin has in high concentrations (Hamre and Rake, 1947) Rake (1948) reported that streptothricin and streptomycin were valueless while the [illegible]

was frequently effective in climatic bubo although fluctuant buboes required aspiration

References

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[illegible] 87–501
[illegible] 34
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(3) Oral antibiotics

(a) Aureomycin

Reports concerning the oral antibiotics are equivocal Wright *et al* (1948), employing 10–20 mg of aureomycin daily by intramuscular injection to a total of 160–1000 mg , had good results on eight patients with buboes and three with proctitis, although one relapsed and was retreated Of 14 [illegible] although

patients treated with 1 g of aureomycin given orally daily for one week Benhamou *et al* (1949) Willcox (1950), and Norman (1951) each had success with one case the first of these was confirmed pathologically and had proved resistant to sulphonamides

5 25–85 g orally In six the lesions had been present for less than six

report by the same team (Greenblatt *et al* (1950)) it was stated that of 13 early cases treated there were only four successes, and that the most favourable results were to be obtained in the usually female cases with rectal stricture or proctitis Schamberg *et al* (1951) treated 24 early cases with 7–20 g of aureomycin orally over seven days Nineteen others three with inguinal adenitis, two with proctitis and 14 with rectal strictures, were treated by Fletcher *et al* (1951) with 28 70 g Early cases showed encouraging responses but the results in late cases were not so successful Twelve Negro women with rectal strictures were treated with aureomycin by Banov (1951) all reported subjective improvement within a few days and remained improved over 11–18 months Aureomycin was also given to 22 others with rectal stricture by Wright and Prigot (1951)

(b) Chloramphenicol and Terramycin

Chloramphenicol was tried by Greenblatt *et al* (1950) but was considered inferior to aureomycin There was no improvement in four early cases and in only one of five late cases treated Chloramphenicol however, proved curat

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ferred 4 g daily for 10–20 days Four cases of stricture of the rectum were given aureomycin or terramycin by Andrea (1950) with improvement

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CHAPTER IV

NON-GONOCOCCAL URETHRITIS AND REITER'S SYNDROME

A. NON-GONOCOCCAL URETHRITIS

(1) General

This disease has a world-wide incidence A comprehensive review of the main causes of this condition was given by Harkness (1950) and also by Coutts *et al* (1951) Non-viral urethritis was considered by Guilleret and Pellarat (1951) and non-venereal urethritis by Harkness (1950*a*)

With the

numbers of new patients so afflicted who attend the clinics of England and Wales In 1951 there were 10,794 cases compared with 14,975 male cases of gonorrhœa

For some time the disease was not regarded in the United States as of such great

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regarded as a serious problem amongst the American forces occupying Japan, however, where, in the U S Air Force, there was an incidence of 23 9 cases per 1,000 (Baier, 1949), and latterly in the U S Army at home (Graham, 1952)

Willcox (1949) contrasted 86 patients suffering from non-specific urethritis with 50 others who had non-venereal skin complaints No less than 52 3 per cent of the urethritis group had had venereal disease before admission as against 8 per cent of the controls The urethritis group was generally more promiscuous and more unstable psychologically Injection of whole blood into the urethra failed to provoke a discharge in 11 recently cured persons Forty-three cases of non-gonococcal prostatitis were reported by Riedel (1951), who noted that there was sometimes a fall in blood pressure following prostatic massage.

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Guilleret, P, and Pellarat J (1951) *Bull Soc franç Derm Syph*, 58, 125–43
Edinburgh, Livingstone

–51

(2) Bacteriology

Of 475 cases of non gonococcal urethritis amongst U S troops in Japan reported by Baier (1949) no less than 79 per cent were believed to be bacterial in nature—a considerably higher percentage than is generally encountered in Britain where the so called 'abacterial' urethritis is ex-

and which is not usually cured by penicillin Only saprophytes such as *S albus* and diphtheroid bacilli were noted, and these were regarded as contaminants Weckstein and Rasmussen (1946) likewise made cultures of the prostatic fluid of 100 patients with this condition In over 68 per cent *S albus* was present, and 65 per cent of the organisms were resistant to penicillin, 69 5 per cent to neoarsphenamine and 95 per cent to powerful concentrations of sulphadiazine

Coutts and Vargas-Zalazar (1946) examined by dark field the centrifuged deposit of the urines in five cases of abacterial pyuria and found spirochætes resembling *S dentium* They considered that these may have arisen from the teeth or alimentary system One such case was reported by Czekalowski and Horne (1951) The diversity of the organisms and parasites which apparently may cause non gonococcal urethritis, and the not infrequent finding of spirochætes on dark field examination of the discharges, with the possibility of buccal or anal coitus being responsible for this, was stressed by Coutts (1948)

The ætiology of non-specific urethritis is not yet fully understood *Trichomonads* have often been considered (Fieldsend, 1946), but although found in some cases, have not so far been seen sufficiently often to be regarded as the primary cause Recently investigations have been concentrated on pleuro pneumonia like organisms (P P L O) and on the inclusion like bodies which may be observed in Giemsa stained urethral scrapings

An important monograph is that of Harkness (1950) which describes in detail the protean list of causes and includes some excellent colour drawings of the so called virus inclusion bodies and pleuro pneumonia like organisms which may be found in urethral scrapings of sufferers from this condition—the latter more easily in cultures from urethral washings Pleuro-pneumonia like organisms were cultured in 21 of 57 cases of sub
il urethritis, and in 7 of 41 with Reiter's syndrome or
/arthritis by Harkness and Henderson Begg (1948) Nega

tive results were obtained in 50 normal males The significance of pleuro-pneumonia like organisms [illegible]

of ba [illegible]

Sm [illegible]

which required serum or ascitic fluid A method of concentrating the growth factor of these organisms, which occupy a position between the rickettsia and the bacteria, was also described Morton *et al* (1951) found P P L O in 21 of 85 persons attending a urological clinic and they were found in 50 per cent of 22 cases of abacterial urethritis Morton *et al* (1951*a*), however, found them also in the saliva of 46 of 100 subjects Smith and Morton (1951*a*) found them in 38 (33 6 per cent) of 114 throat [illegible]

[illegible] (1952), in Stockholm, grew P P L O in cultures from 18 per cent of 61 men with non gonococcal urethritis, 3 per cent of 31 patients with acute untreated gonorrhœa, but also from 17 per cent of 60 normal subjects Moreover Melén and Odeblad (1952) found them in 8 of 45 healthy women but not in 13 virgins In non pregnant patients they were found during the first ten days of the menstrual cycle Latterly Ruiter and Wentholt (1952) have found them in four cases of genital fuso spirillary infections Norman *et al* (1950) found that sera from 18 cases of non-specific urethritis failed to agglutinate five human strains of P P L O

The evidence in [illegible]

[illegible] found inclusions in a number of cases [illegible]

dozoa (the [illegible]

conjunctivitis [illegible]

seen in non gonococcal urethritis resemble, was presented by Thygeson (1951) Similar bodies have also been described in the disease enzootic abortion in ewes by Stamp (1951) and Stamp *et al* (1950)

The relationship between inclusion urethritis, lymphogranuloma venereum and inclusion blennorrhœa was well summarized some years ago by Harrison and Worms (1939) On the other hand Bedson (1950) examined the discharges of 25 cases of non gonococcal urethritis and could find no evidence of the virus of inclusion blennorrhœa Moreover complement fixation tests for [illegible]

negative, as were the Frei te[illegible]

patients with non specific [illegible]

scratch disease'—another s[illegible]

Later work (1953) revealed no undue incidence of positive complement fixation tests to lymphogranuloma venereum or to enzootic abortion in ewes in the sera from cases of non specific urethritis

Until the virus has been successfully passaged in animals or eggs, the virus nature of this disease must remain unproven

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(3) Treatment

For a number of years sulphonamides have been the mainstay of treatment but have been only fairly successful Thus Willcox (1949) reported 50 per cent success with 42 patients having treatment (mainly irrigations) other than with sulphonamides There was also 50 per cent success in 14 cases treated with sulphonamides alone, but 78 1 per cent success in 69 patients treated with sulphonamides and urethral irrigations combined Graham (1952) reported 90 per cent success in 1,000 patients treated with sulphonamides, but only when an initial dose of 4 g was followed by 1 g every 4 hours

Coutts

which

Penicillin, however, is not particularly effective in non gonococcal urethritis and streptomycin, aureomycin and the other oral antibiotics are generally employed Although most striking successes can on occasion be achieved with *streptomycin* its over all results are disappointing Pulaski (1947) noted three clinical failures in six patients treated Harkness (1949) had only six cures in eleven treated with 0 5–1 5 g of streptomycin, while Willcox (1949*a*) treated seven cases with single injections of only 0 2–1 0 g with response in four If it is used at least 1 g should be given daily for four days

The results obtained with the oral antibiotics have been much better Harkness (1949) had seven out of ten cured with *aureomycin*, and three of four cases treated by Willcox and Findlay (1949) also responded Six intractable cases were successfully treated with 4–6 g of aureomycin by Thomson (1951) McVay *et al* (1951) reported eleven other cases successfully treated with this drug and gave detailed reports of four cases in which trichomonads were found

Using *chloramphenicol* Chen and Dienst (1950) saw improvement or recovery in five patients who had 3 6 g of chloramphenicol over 1–2 days Personal experience suggests that the effective dose of all the oral antibiotics is 6 g or above over 4–6 days Findlay and Willcox (1951) treated twelve patients with chloramphenicol and three of their female consorts Inclusion bodies were found before treatment in eight and P P L O in five There were four treatment failures

Willcox (1951) and Willcox and Findlay (1952) reported 20 cases treated with oral *terramycin* with only one failure The former author (1951*a*) described the minor side effects of this drug including the syndrome of anorectal burning and pruritus

At the Venereal Disease Symposium held under the auspices of the National Institute of Health and the American Venereal Diseases Association at Washington in May, 1952, Willcox and Findlay (1952*a*) presented data concerning 50 male cases, including four cases with Reiter's syndrome, plus six female consorts, treated with 2 5–19 25 g terramycin The clinical results were excellent, only four patients, including two of those with Reiter s syndrome, proving resistant and six showed relapse reinfections There were only seven failures in the 46 persons receiving 5 g or more (15 2 per cent) 'Inclusion bodies', which were found in 42 patients before treatment, disappeared from all but one male and one female case

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B. REITER'S SYNDROME

(1) General

Although Reiter's syndrome and non specific urethritis are considered separately in this book, it is not yet known for certain whether Reiter's syndrome has a separate ætiology or whether all afflicted with 'abacterial' urethritis are potential sufferers

The condition was reviewed by Harkness (1947) and again by the same author (1949), based on a personal experience of 126 cases Nine cases were reported by Morrison and Thompson (1948), six cases from America by Coodley *et al* (1948), one from Canada by Ffrench and Mador (1950), one from Australia by Fletcher (1948) and 30 cases from Scandinavia by Lövgren and Masreliez (1949) The latter showed well the tendency of the complaint to relapse, often after considerable periods of time Recurrences were noted in no less than 56 per cent, and one case had six relapses in six years The syndrome was noted in a boy of four years in New York by Florman and Goldstein (1948), while keratosis blennorrhagica, which is unusual in women, was noted in an Indian girl aged seven years by Gault and Gault (1946), and also in an English boy aged nine by Corner (1950) Of 106 cases of arthritis associated with urethritis seen by Levy (1950) in Malaya, 47 were associated with gonococcal urethritis and 57 with non-gonococcal urethritis 45 gave a negative gonococcal complement fixation reaction

A case of keratosis blennorrhagica was presented by Auckland (1951), who on the basis of the histological appearances considered the condition to be a form of psoriasis The literature of this interesting condition was extensively reviewed by Ladany and Hughes (1946)

[illegible]

bacillary dysentery has been well made out, and it is probable that persons suffering from what was once termed 'dysenteric arthritis' were really affected by this condition Paronen (1948), in Finland, in a lengthy paper

with no less than 150, mainly Continental, references, described 344 cases of

ulcerated bowel is but one of the portals of entry of the virus, for no such

recently recovered from Reiter's syndrome, two of whom had had con-

Progressive loss of vision occurred in 91 per cent and 67 per cent showed total loss of vision in at least one eye Two cases of Behcet's syndrome were reported by Csonka (1947), and six cases of Stevens-Johnson syndrome (erythema exudativum multiforme) were described by Thomas (1950)

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2)

1, 483–4

(2) Bacteriology

Both inclusion bodies and pleuro-pneumonia like organisms are frequently reported *together* in urethral scrapings from cases of Reiter's syndrome, but the significance of these findings is not yet clear Pleuro-pneumonia-like organisms, however, could not be detected in the urethral, nasal or

joint secretions of two such persons tested by Lövgren and Masreliez (1949)

Dunham *et al* (1947) claimed successfully to have cultured the virus of Reiter's syndrome in eggs, the virus was found to be capable of producing conjunctivitis when inoculated into mice

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(3) Treatment

Definitely before the introduction of the antibiotics, and probably also today, pyretotherapy is the most successful single treatment measure for patients with Reiter's syndrome Five cases were successfully treated by [illegible] (1948) [illegible] Willcox *et al* (1947) [illegible] l pyuria and Reiter's syndrome, tried neoarsphenamine for the latter Although the joint manifestations were not benefited he considered that the drug was of some value The drug, however, is too toxic for only a dubious result

The literature of keratosis blennorrhagica was extensively reviewed by Ladany and Hughes (1946) who reported one case resistant to *penicillin* Two cases, however, in which there was apparently a good response to penicillin were recorded by Freireich *et al* (1947), and Hiehle and Hamp (1949) reported a case of Reiter's syndrome with keratosis blennorrhagica treated with this drug Davies (1949) likewise reported a case successfully treated with penicillin Warthin (1948) treated four cases with *streptomycin* with some success, Thompson *et al* (1949) had success in one case given 40 g of streptomycin over 16 days, and Korb and Brown (1950), and Griep and Leich (1951) each had a good result in a case treated with *aureomycin* Findlay and Willcox (1951) also reported success in one case treated with *chloramphenicol* and Willcox and Findlay (1952) in two of four cases treated with *terramycin*

Single case reports, however, tend to give a false picture and Reiter's syndrome is a condition of varying intensity The upshot of treatment with the oral antibiotics is frequently disappointing

The results obtained with ACTH and cortisone are of more interest Ogryzlo and Graham (1950) treated three cases with 10–25 mg of ACTH every 6 hours for 12 14 days Improvement was noted in all, but there was a tendency to relapse after the treatment was concluded

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CHAPTER V

SOFT SORE (CHANCROID) AND OTHER CONDITIONS

A. SOFT SORE

(1) General

THE so called 'syphilization' treatment of the last century, which was practised amongst others by Boeck of Oslo, in an attempt to immunize against syphilis by the inoculation of matter from the sores, and by repeated passage in the person so treated, was recalled by Erichsen (1951). At that time the distinction between chancroid and chancre was not fully understood and the patients were really acquiring multiple lesions of soft sore. In England and Wales in 1951 only 437 male and 16 female cases of soft sore were reported from the clinics.

The present day high incidence of chancroid in the Gold Coast and in Southern Rhodesia was emphasized by Willcox (1951, 1951*a*, 1952, 1952*a*) who described the skin testing of 1,022 Africans with Dmelcos (*H. ducreyi* vaccine). The percentage of positives was much higher in the towns than in the rural areas (Table 3). The skin test (Ito Reenstierna

TABLE 3

REACTIONS TO THE ITO REENSTIERNA TEST FOR CHANCROID IN THE GOLD COAST AND SOUTHERN RHODESIA

Region	Group tested	Number tested	Number positive	Percentage positive
Gold Coast				
Accra	Chancroid patients	10	9	90.0
Accra	Other venereal disease patients	22	10	45.5
Southern Rhodesia				
Salisbury	Male chancroid patients	32	20	62.5
[illegible]	[illegible]	290	129	44.5
		66	12	18.2
		168	41	24.4
		61	4	6.6
		90	35	38.9
		150	7	4.7
		14	5	35.7
		119	6	5.0
Total		1,022	278	27.2



FIG 4—GENITAL ŒDEMA IN LYMPHOGRANULOMA VENEREUM See p 34
(Dr W E Coutts Chile)



FIG 5—EXPERIMENTAL CHANCROID IN MAN See p 53
(Resulting from intradermal injection of bubo fluid)

reaction) was found by Reymann (1951) to give extremely specific results in Denmark

Dienst and Gilkerson (1947) tested for chancroid, by means of smear, culture and skin test, 116 patients with penile lesions in which syphilis had been excluded Films and cultures were negative in 37 6 per cent, and skin tests in nearly half, including 33 patients in whom Ducrey's bacillus had previously been found in smear or culture In these cases involvement of the regional glands was slight Of the series as a whole, and in 207 other cases with penile lesions, about one half reacted Of 103 patients with active glandular enlargement 98 per cent reacted to the Ducrey skin test for soft sore or the Frei test for lymphogranuloma venereum, or both

Culture of *H ducreyi* was considered by Reymann (1949), and Dienst (1948) reported that such cultures became avirulent for rabbits and man when subcultured for several months on defibrinated rabbit's blood Lyophilized cultures, on the other hand, remained virulent after storage for eighteen months at room temperature The antigenic power of cultures when used for the skin test does not apparently depend on their virulence

Caletti (1946) demonstrated an antagonistic action between *para* aminobenzoic acid ointment and vaccine in chancroidal lesions Experimental lesions of chancroid were cured by three to four intravenous injections of a vaccine containing Ducrey's bacillus If 10 per cent *para* aminobenzoic acid ointment was applied to the lesions before and during this treatment with vaccine the ulcers did not heal This phenomenon was observed in a patient with two experimental lesions, the one not so treated healed while the other did not

Wetherbee *et al* (1949) tested a number of antibiotics *in vitro* against 16 strains of *H ducreyi* and reported that streptomycin was the only one likely to be of value This was, however, not found to be the case in the treatment of the clinical infection

Willcox (1950) tested numerous drugs against the experimental infection [illegible]

which had been proved by previous inoculation into others, were first treated with the drugs to be tested and then, 24 or more hours after treatment had commenced, the fluid was aspirated and its virulence again tested by inoculation into volunteers Thus both the prophylactic and curative possibilities were investigated These experiments, which with the controls involved some 227 inoculations (1952*b*), gave essentially the same results Sulphonamides, streptomycin, penicillin in high doses, aureomycin and chloramphenicol were all effective, but neoarsphenamine, bismuth and the antimonials were not (Table 4)

TABLE 4

EXPERIMENTAL CHANCROID IN MAN

Treatment	Total persons inoculated	'Takes'	No 'takes'	Percentage 'takes'
Controls	36	32	4	88 9
Sulphonamides	36	1	35	2 8
Streptomycin	21	0	21	Nil
Aureomycin	24	2	22	8 3
Chloramphenicol	10	0	10	Nil
Penicillin				
POB alone (8 daily injections)	32	0	32	Nil
POB with sulphonamide	2	0	2	Nil
*PAM (single injections)	21	9	12	42 8
Oral	4	1	3	25 0
Neo arsphenamine	38	25	13	65 8
(Bismuth) †	(3)	(2)	(1)	66 6
Antimony	3	3	0	100 0
Total	227	73	154	

* *Among ten persons whose inoculations took place within 0–4 days after being* given 2 4 mega units of procaine penicillin with 2 per cent aluminium monostearate there were only two 'takes', while of eleven persons receiving inoculations 5–8 days after injection 'takes' were noted in no less than seven

† 3 patients had both bismuth and neoarsphenamine

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(2) Treatment

A course of sulphonamides has for some years been the standard treatment for chancroid and the results have been fairly satisfactory Willcox (1952) reported that the sores of 100 male Africans treated in the Gold Coast in 1943–5 with sulphonamides healed in an average of 12 5 days, while those

of 94 Africans similarly treated in Southern Rhodesia during 1949 healed in an average of 12 7 days Harp (1946) reported 300 cases treated with

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they

may, therefore, be given with impunity without risk of incompletely curing syphilis should it escape recognition

Penicillin, for this reason, is not a suitable drug to employ for the individual case of chancroid although, if given in sufficient dosage, it is effective Lahiri (1947) treated 32 cases of chancroidal bubo with systemic penicillin and claimed cures within 2–4 days, but wisely recommended that cases so treated should be followed up for two years, which is a considerably greater inconvenience than the mere three months required following treatment with the sulphonamides Pereyra (1948) gave penicillin by local iontophoresis to 13 patients with chancroidal ulcers, apparently with successful results However, when patients are being treated in the mass (e g in Africa), without proper diagnostic aids to exclude syphilis, and a proper follow up is impossible, there are some advantages of having a standard treatment for all cases of penile sore Willcox (1950) satisfactorily treated 99 Africans suffering from genital sores, of whom 19 were considered to have chancroid uncomplicated by syphilis, and the remainder syphilis with and without chancroid, with single injections of 2 4 mega units of procaine penicillin with 2 per cent aluminium mono stearate It was considered that this method of treatment was of great administrative value under African conditions where dark field diagnosis was not available

Mortara and Saito (1946) showed that *H ducreyi* was sensitive *in vitro*

30 weeks and there was only one possible recurrence at six weeks

Subsequently Jawetz (1948) successfully treated three cases with a total of 10 g given 6 hourly for 5 days, and Weber *et al* (1949) had success in one case which had proved resistant to sulphonamides Taggart *et al* (1949) treated 42 cases of chancroid with 1–2 g of streptomycin daily for 5–19 days with good results in in patients, but they were less fortunate with 19 others given 2 g daily for 6 days (omitting Sundays) as out patients Sulphonamides were, therefore, still preferred Rollier and Maury (1950) reported good results with as small a daily dose as 0 5 g

Willcox (1950*a*) also treated with streptomycin eight cases in African negroes with 1 5–5 0 g given over 2–9 days The sores healed in 6 days and, as is usual, the buboes required aspiration when they became fluctuant There was only one known relapse Also treated were three cases of dark field positive early syphilis with 2 0–4 5 g of streptomycin over 4–9 days

Treponemata disappeared slowly from the lesions but the sores all healed without other measures thus indicating that this drug too *may* mask syphilis

Zheutlin and Robinson (1950) successfully treated three cases of chancroid with 2 g of *aureomycin* daily for 7–14 days, while seven of the patients with early syphilis treated with aureomycin by Olansky *et al* (1950) were believed to have double infections with soft sore, and the lesions healed in all Greenblatt *et al* (1950) considered that as little as 5–10 g of both aureomycin and *chloramphenicol* may be sufficient for this disease Willcox (1951) treated one case with 2 25 g of chloramphenicol and two others with 2 g of aureomycin spread over 3 days The sores healed although fluctuant buboes still required attention It was shown that the bubo fluid of treated cases rapidly became avirulent when inoculated into volunteers Four cases of chancroid were treated with *terramycin* by Niedelman *et al* (1951) and 4 g a day for 5 days was considered a suitable course, as it is probably also for chloramphenicol and aureomycin

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58 9
: 71–2

B. BALANO-POSTHITIS

is not recommended as it is prejudicial to the exclusion of syphilis by dark field examination.

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C. CONDYLOMATA ACUMINATA

Podophyllin, in oily or watery suspensions, in alcoholic solutions or in a [illegible] ses, continues to be an excellent [illegible] embranes Sullivan and King [illegible] using 25 per cent podophyllin [illegible]

[illegible] Ibarra (1950) With phimotic subjects, however, severe local reactions may sometimes occur Paulosky and Leider (1949) stated that this may be obviated if Fowler's solution is applied instead three times daily for 3 days and thereafter once daily A slower cure results, but it still may be expected within two weeks Flowers (1951) described three patients on whom a Cæsarean section had to be performed because warts filled the vagina

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Flowers [illegible]

[illegible] 47

D. TRICHOMONIASIS IN THE FEMALE

Trichomonas vaginalis was found in 30 (5 3 per cent) of 562 women attending a birth control clinic by Whittington (1951) That the lavatory seat is a possible agent of transmission was emphasized by McCullagh (1949) Kessel and Thompson (1950), in a study of the survival potentialities of the parasite, considered that fomites under natural conditions might act as carriers

A study of trichomonads in relation to *beta* glucuronidase activity was conducted by Kasdon *et al* (1951) A simplified culture medium was described by Lash (1950)

The many different local treatments recommended for this common and often troublesome complaint are a testimony to the somewhat unsatisfactory

nature of all Many discharges clear up, but many relapse Ninety four of 100 patients described by Hundley *et al* (1950) were considered cured by Tetronyl Of 39 treated by Hensel (1950) with a vaginal cream con sisting of 2 per cent allantoin, 15 per cent sulphanilamide and 0 2 per cent *para* amino acridine, only three required retreatment Sulphathiazole jelly was used on 169 cases of trichomoniasis and 139 cases of vaginal thrush by Karnaky (1951) A considerable degree of success was claimed with 600 women by painting with 75 per cent mercurochrome by Ferguson and Edgerton (1950)

Penicillin pessaries have not proved useful The parasite disappeared in less than half of the cases so treated by Walter *et al* (1951)

More hopeful results are, however, obtained with pessaries containing aureomycin, chloramphenicol or terramycin Of 37 patients treated with aureomycin locally by Greenblatt and Barfield (1951), 29 were still well after one month McVay *et al* (1949) used aureomycin in insufflation on 54 patients Willcox (1952) has has had some success with the vaginal instillation of an ointment containing 30 mg of terramycin per g

Acetarsol pessaries continue to be widely used and a fairly satisfactory

in all but one case One patient even had a Herxheimer reaction The same is of course possible if aureomycin, chloramphenicol or terramycin is employed (See non specific urethritis, pp 44–5)

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CHAPTER VI

EXPERIMENTAL AND ANIMAL SYPHILIS

(1) GENERAL

McLeod and Arnold (1949) showed that a suspension of *T. pallidum*,
stored at minus 70°
remain viable for a
spirochætes to cher

acids

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2, 307–16

(2) CULTURE OF TREPONEMES

reported to be

Nichols, Reiter, Kazan, Noguchi and other strains were not, and that these never had been, *T pallidum* They have, however, done yeoman service in research and continue to do so.

T. pallidum outside the body by means of tissue culture. Maintenance of (1949), employing the Nichols strain and a very complex medium, maintained the organism *in vitro* for as long as 97 days. The easier culture of the

Reiter spirochæte was described by Gelperin (1949) Growth promoting factors for the Reiter treponeme (pathothenic acid, glutamine and phenyl alanine) were considered by Steinman and Eagle (1950) Rose and Morton (1952) described a convenient medium for the cultivation of the Nichols, *Kazan and Reiter strains consisting of Bacto-Heart infusion, broth,* glucose, neutralized cysteine and plasma filtrate

Newcomer and Haanes (1949) reported the successful cultivation of the Nichols strain under anærobic conditions in chick embryos, as did Beardmore and Dodd (1950) A further report by Haanes *et al* (1950) described further success with the Kazan strain Haanes *et al* (1952) employed cultural methods in order to determine whether filterable forms existed *None were found in the Nichols or Kazan strains of T pallidum,* or in *Bor anserina*

It is interesting to note from Soviet Russia that Vyascleva (1949) studied *human* strains said to have been grown on 'Kitt Tarozzi medium'

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[illegible] 33, 318–22

[illegible] 52

(3) ANIMAL SYPHILIS

(a) General

The rabbit has been the animal most used in experimental studies An orchitis is produced following intratesticular inoculation and latent infections can be confirmed by killing the animal and inoculating crushed lymph nodes intratesticularly into other rabbits McLeod and Arnold [illegible] intratesticular inoculation [illegible] *al* (1950 1952) noted that [illegible] h the Nichols strain con[illegible] after the animals became asymptomatic Marcus and Kahn (1947) noted that the Kahn test in rabbits tended to become stronger as the age of the animal increased

after intratesticular transfer (Rosahn *et al*, 1948) Thus if both the rabbit and the mouse are used together results may be obtained much quicker than by using the rabbit alone

Vaisman (1950) found that [illegible]

W [illegible]

r [illegible]

inoculated mice, but that such brains were capable of producing intratesticular lesions when transferred to rabbits The possibility of infravisible forms was considered

Magnuson *et al* (1949) showed that different strains of mice differed widely in their susceptibility to syphilis, and that the tissues involved had the following order of susceptibility spleen, liver, brain, blood, and lymph node Rosahn and Rowe (1950) showed that if mice were inoculated with *T pallidum*, and an attempt was later made to infect rabbits from them, it was necessary to inject ten times as many *T pallidum* if the attempt to infect rabbits was made 10–13 days after inoculation, than if it was made at 81–92 days From this it was deduced that the period of division of the treponeme in the mouse might be as long as 24 days For the rabbit, however, Cumberland and Turner (1949) suggested it might be as short as 33 hours

The golden hamster, as an alternative to the rabbit or mouse, was tested by Johnson (1949) and found suitable

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(b) Immunity

Rabbits fed on cholesterol develop atheromatosis of the aorta, aortic valves, coronary arteries and, especially in albinos, a xanthoma of the iris in which an iritis commonly develops after an experimental syphilitic infection (Frazier *et al*, 1948)

The involvement of the central nervous system in the mouse by

treponemata, which may then show neurotropic properties in the rabbit, was discussed by Schlossberger (1948)

In rabbits the size of the inoculum influences the possibility of a 'take' Magnuson *et al* (1948) showed that as the size of the inoculum was

developed the most lesions Schipper and Chesney (1950) stated that those so inoculated developed the highest titre of reagin in the blood Wiggall and Chesney (1950) *considered that the size of the inoculum injected* intravenously had no effect on the course of experimental syphilis in the rabbit

Eagle *et al* (1947) showed that the amount of penicillin required to prevent syphilis in half of the rabbits given a fixed inoculum of *T pallidum* remains constant for four days, but at the end of the second week was seven times, and at the end of six weeks thirty times as much

Hollander *et al* (1952), working on rabbits, believed that the usual course of a syphilitic infection is determined by a regular logarithmic *increment of treponemes, which continue until sufficient are present to* produce a lesion A single subcurative treatment therefore, interrupts an orderly process, causing it to revert to an earlier stage before resuming its usual course

Rosahn and Rowe (1950) showed that if mice were inoculated with *T pallidum*, and an attempt was made later to infect rabbits from them, it was necessary to inject ten times as many *T pallidum* if the attempt was made 10–13 days later than 81–92 days later

periods of 6–20 months after infection

Magnuson *et al* (1947) failed to immunize rabbits by the injection of dead *T pallidum* although positive serum reactions were induced Lyophilized spirochætes given intracutaneously over 12 weeks by Waring and

perhaps some minor immunity

Inoculation of dead spirochætes into rabbits was shown by Eagle and Fleischman (1948) to produce positive serum reactions in the recipients but without further immunity to the experimental infection Gelperin (1951) tried to protect rabbits against virulent *T pallidum* by inoculation of the Reiter spirochæte This was also unsuccessful although the incubation period was prolonged and the lesions were reduced in size Infection with *luttoni* was introduced into the eye of the rabbit by Levaditi and man (1950), but this failed to protect the eye against *T pallidum*

Since the introduction of penicillin for the treatment of human syphilis there has been increased incidence of reinfection after the completion of treatment One possible explanation for this is that the patients are returning more quickly to the same sexual environment, and another is that some degree of immunity used to be conferred on the patient who was treated by the older m

Magnuson *et al* (1950) hypothesis by comparing cured rapidly by large dc given subcurative doses for some weeks before the administration of the curative dose

Magnuson and Rosenau (1948) showed that if rabbits were cured at increasing intervals after infection the ability to reinfect with syphilis was proportional to the length of time before the first infection was treated

Arnold *et al* (1947) showed that rabbits could invariably be infected only ten days after the completion of penicillin treatment of experimental syphilis of 6–8 weeks' duration, although if the rabbits were left untreated no such reinfection could be produced The same authors (1947*a*) reinfected rabbits ten days after the completion of treatment with penicillin for syphilis of eight months' duration None developed a chancre at the site of inoculation but 53 per cent had a symptomless invasion—a much higher rate of local protection than is noted in early syphilis

Arnold *et al* (1950, 1950*a*, 1950*b*) have produced other evidence to suggest that immunity to early syphilis increases with the duration of the disease before treatment Cumberland and Turner (1949) showed that the spirochaetes multiply more slowly in immune' animals

Magnuson and Thompson (1952) showed that successive infections with syphilis in rabbits produced no significant increase of immunity over that produced by the first infection, the immunity being much less than that produced by a single untreated infection of the same total duration

Turner *et al* (1948) found that sera from patients with secondary or later syphilis exert an inhibitory effect when injected intradermally into rabbits simultaneously infected with syphilis non syphilitic sera did not show the same effect

Magnuson *et al* (1951) showed that the castration of rabbits of either sex prolonged the incubation period and increased the resistance to the experimental infection

The whole problem of immunity is now being re-examined in the light of new but incomplete knowledge of cortisone and ACTH Turner [illegible]

(DeLamater *et al* (1952) considered it was not hyaluronic acid alone) The lesions continued to enlarge slowly and ultimately ruptured to discharge their contents Dark field examination showed an abundance of *T pallidum* in this material, and these were present in greater profusion than in the controls They were virulent on passage and susceptible to immobilization Withdrawal of the cortisone was followed in 2–7 days by a 'rebound phenomenon' associated with a reappearance of the erythema and induration, followed by enlargement of the lesions In a small series tested the titre of reagin in the sera of the animals treated with cortisone was significantly lower than was expected

Cortisone thus produces a marked change in the host parasite reaction Spirochætes multiply but the host response is lessened It was considered that cortisone might be dangerous to give to human patients with cardiovascular syphilis owing to the possible risk of the 'rebound phenomenon' DeLamater *et al* (1952) studied the effect of cortisone on experimental syphilis in the rabbit, and upon experimental spirochætosis in the chicken In both diseases there was an increase in the numbers of ... Sheldon *et al* (1952) ... , the Herxheimer reaction

There thus appears to be some connexion between the action of cortisone and ACTH and hyaluronidase—the spreading factor which acts upon the ground substance to produce an environment favourable to ... on the rôle of hyaluro- ... l the same author (1950) ... tion of syphilitic lesions by the injection of hyaluronidase into the skin and eye of the rabbit ...

exposed to testicular hyaluronidase

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(c) Drugs

Arsenic

Probey (1947) reported that the sulpharsphenamines were slightly more spirochæticidal than the neoarsphenamines but, by arsenic content, the arsenoxides were more effective than the arsphenamines The same author (1948) found that the Nichols strain was not made resistant by repeated sub-curative doses of neoarsphenamine

Synergism between fever and arsenic was noted by Carpenter *et al* (1947)

Kroó (1949), working with plasma of chickens infected with *T gallinarum*, showed that when such material was treated *in vitro* with phenylarsenoxide before injection into newly hatched or mature chickens, the newly hatched birds became infected but the mature birds did not.

Penicillin

Synergism in the rabbit between penicillin and bismuth was noted by Magnuson and Rosenau (1948), and by Levaditi and Vaisman (1950) Kolmer (1948) noted synergism between penicillin and bismuth given orally Ovchinnikov and Kuchinskaya (1948) reported that the admixture of penicillin and bismuth before injection had a retarding effect on the absorption of penicillin

Eagle *et al* (1947*a*) reported synergism between penicillin and fever, stating that the curative action of penicillin was increased tenfold if it was given concurrently with a 10 hour fever session

Rosahn and Rowe (1950) showed that penicillin G was three times as effective as sodium penicillin in suppressing syphilis in the mouse, and about twenty times as effective as penicillin X The dose of penicillin to cure 50 per cent of animals with mouse syphilis, given as penicillin in oil beeswax over a period of 4 days, was calculated by Magnuson and Rosenau (1948*a*) to be 14,000 units per kilo, as against 64,000 units per kilo to cure 90 per cent of the animals

of treatment was also prolonged Rosahn and Gueft (1947) illustrated this point by noting that, when the number of daily injections was increased from eight to sixteen, the total curative dose was unaltered

Eagle *et al* (1950) suggested that it is the aggregate time, not necessarily continuous, during which penicillin is detectable in the blood, which is the important factor in penicillin therapy

That some batches of penicillin G may be more potent in rabbit syphilis than others was suggested by Arnold and Thayer (1951)

Streptomycin

produced by this means much quicker than by allowing the experimental infection to develop before treatment by the drugs concerned, and following this by prolonged surveillance, gland transfer and the observation of a new set of animals Using such a technique Rake *et al* (1947) found

be achieved by giving 24,000–25,000 units per kilo over a period of 5 days Penicillin was curative in a dose of 15,000 units per kilo The limited

powers of streptomycin in animal syphilis were also shown by Bessemans and Derom (1950)

Other antibiotics

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fraction that of bacitracin (Eagle *et al*, 1948)

Vyaseleva (1949) reported that *gramicidin* had negligible spirochætostatic action and *aspergillin* had none The limited antibiotic properties of *tyrothricin* were shown by Bessemans and Derom (1950) Experimental work with *terramycin*, either alone or in combination with Mapharsen and bismuth, was described by Kolmer (1952)

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CHAPTER VII

DIAGNOSIS OF SYPHILIS

A. MICROSCOPY

THE principles of dark field microscopy were reiterated by Reynolds and Hesbacher (1950) Jahnel (1949) also considered the dark field microscope and pointed out the value of linking two instruments so that the movements of suspected *T pallidum* in one might be compared with those of known *T pallidum* in another.

DeLamater *et al* (1950*a*) and Rosahn and Freeman (1952) described a new staining technique for *T pallidum* based on Fontana's method Likewise new staining techniques were described by Campbell and Rosahn (1950), by Onoda (1951), and by Levine (1952) A technique of performing dark-ground illumination of unstained smears for the recognition of *T pallidum* was described by Coutts *et al* (1952, 1952*a*)

McFarlane (1950) presented recent advances in microscopy, including those of the phase contrast and electron microscopes The phase contrast microscope was used by DeLamater *et al* (1950, 1950*b*, 1950*c*, 1951, 1951*a*, 1951*b*, 1951*c*) to study the life cycle of spirochætes They published photomicrographs depicting the Nichols, Kazan, Noguchi and human strains of *T pallidum* showing that these treponemes multiply, not only by transverse fission but also by formation of buds, or gemmæ, which develop into spirochætal cysts in which single spirochætes differentiate Studies of the Nichols and Reiter strains were made under the electron microscope by Morton *et al* (1951) and striking photomicrographs were also published with this paper These show numerous flagellæ, growing in clusters from points immediately adjacent to the ends of the treponemes

under the electron microscope, and found lengthening of the organisms with chain formation Both the dark phase contrast and electron microscopes were used by Rose and Morton (1952) to show the many morphological variations of a number of experimental strains of *T pallidum*

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B. SERUM TESTS

(1) General

A quarter of a century of serology was reviewed by Kahn (1948), and modern developments were considered in general terms by Price (1949), by Mahoney and Zwally (1949), and by Puccinelli (1951) Diagnostic problems and serological tests were considered by Rein and Kostant (1952)

(1949) Alaerts (1946) was able to obtain a positive Meinicke reaction from aqueous humour

Rein and Kostant (1949) discussed antigens and antibodies in the serology of syphilis D'Alessandro *et al* (1950) considered antigens prepared from cultured strains of the treponeme Paoletti (1950) also described serum tests performed with spirochætal antigens and stated that they

that it reacted strongly when fresh with about 80 per cent of strongly positive syphilitic sera, but when stale was unsuitable American work on

The use of camphor to increase the sensitivity of serum tests was discussed by Saint Prix and Mutermilch (1949) The value of standardization of reagents in the Canadian Provincial Laboratories was emphasized by Allen (1948)

Taran (1946) showed that 200 anti-complementary sera could be made fit for testing by saturation with undiluted complement, and incubation and inactivation before commencing the test

A comparatively recent development has been the use of frozen sera

maintain its activity *for a minimum of 15 months* by Cannefax (*1951*), and for 50 days after reconstitution

Calloway (1947) considered that the Weltmann serum coagulation

found An electrophoretic study of the serum proteins in syphilis was conducted by Benditt and Walker (1948), and the relation of serum globulins to false positive serum reactions was considered by Neurath *et al* (1947*a*, *b*), Erickson *et al* (1947), Volkin *et al* (1947*a*, *b*) and Putnam *et al* (1947)

A method of diagnostic complement fixation, employing spectro-
ial inspections, was described
the sero-diagnosis of syphilis

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(2) Cardiolipin antigens

Cardiolipin, originally prepared by Pangborn in 1941, is a phospholipin obtained by extraction and purification of fresh beef heart When combined in optimum proportions with lecithin and cholesterol, a highly
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and Mazzini tests With this antigen, only 4 9 per cent of doubtful reactions

were noted on 1,046 sera—a result only bettered by the Eagle test—whereas the other tests showed 7 7–19 3 per cent of doubtful results Negative results were obtained with 224 non-syphilitic sera from malarial patients and 642 other sera which were negative to the Kahn and Mazzini reactions Kline (1947), using the same test, found only 1 per cent of false positives in a large series of malarial patients, whereas 8–24 per cent of false posit
Kline and Mazzini tests
5,556 sera and contrasted
Meinicke and Bordet-Wassermann reactions He considered the cardiolipin procedure more specific than the standard Wassermann and a test which would produce fewer conflicting results in the absence of syphilis

Harris *et al* (1948) described their later experiences with cardiolipin on testing 6,605 sera, and Schmidt (1951) on 1,322 sera, while Levine *et al* (1948) had only seven false positives in 24,877 sera tested Giordano *et al* (1948) found 97 per cent of agreement on 24,085 tests with cardiolipin compared with the standard Mazzini flocculation test Klein and Leiby (1948) compared the V D R L test with the Kahn test on 3,652 sera, and Widelock (1948) with the Mazzini, Kahn and Kolmer Andujar *et al* (1948) performed cardiolipin tests in parallel with the Kahn, Kline and Kolmer on 24,609 sera

4,602 sera resulted in 91 9 per cent agreement in the hands of Singh and Sharma (1951) The effects of an additional four minutes' rotation on the V D R L slide test were described by Machala and Hassler (1951)

The cardiolipin test was compared with the Kline by Klein *et al* (1948), and with the Kolmer by Giordano *et al* (1949) The first British series was described by Price and Wilkinson (1950) The same authors (1952) contrasted the results of testing 2,876 sera by the Wassermann test with cardiolipin and crude heart antigens Blumberg *et al* (1950) compared the results obtained by cardiolipin and tissue extract antigens in over 2,000

antigen

Cardiolipin antigens were applied to the Kahn test by Kahn and McDermott (1948), to the Kolmer by Kent *et al* (1948) and Kolmer and Lynch (1948), to the Hinton by Hinton *et al* (1949), and to the Kline by

Klein *et al* (1950) They were also used by Jayewardene and Velaudapillai (1950)

A modification of the slide test for the titration of antibodies was devised by Osler and Widelock (1948) Harris *et al* (1948*a*) described a tube flocculation test with cardiolipin Flocculation tests with cardiolipin tend to develop zonal reactions, and in an attempt to overcome this, Mazzini (1951) introduced a cardiolipin microflocculation test.

Rosenberg (1949) described the use of dipalmityl lecithin as an ingredient of cardiolipin antigen, while a synthetic lecithin component was used by Kline (1950) Variations in the sensitivity of the lecithins used in the test were considered by Kahn and McDermott (1948*a*), and the standardization of the antigen by McDermott and Kahn (1948) Flynn *et al* (1952) showed that purified lecithins from egg yolk could be used interchangeably for the New York State quantitative complement fixation and slide precipitation tests

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(3) Standard serum tests

Cutler and Harris (1951) performed a battery of tests on 417 patients with primary syphilis There was no one test which detected all of the samples showing serological reactivity, and the highest proportion was detected by a combination of the Kline exclusion and the Mazzini flocculation On stored sera the Meinicke clarification gave the best results and Negro and Borghesio (1949) found it was reasonably reliable after 15 days The examination of post-mortem material with Berger's antigen was described by Haicl (1950)

Complement fixation tests were considered by Price (1950) Osmond (1950), on several thousand sera tested, found 95 per cent of agreement

vas described by Colquhoun (1950) Different methods of performing the test were discussed by Krag and Vogelsang (1948) Richardson's modification of the

result in 117 of 14,952 sera which would otherwise have been reported as negative The Wassermann test was further considered by Penttinen and Helle (1949)

orimeter for the standardization of Wassermann test, was described by) also described how photo electric methods might be applied to the reading of the test Velaudapillai (1950) made a comparison of the Wassermann, Kahn and cardiolipin tests on

sera inactivated at 56° C for 30 minutes and at 60° C for three minutes There were few differences in the results of the Kahn test, but those of the Wassermann were inferior at 60° C

The complement for the Wassermann test was considered by Demanche (1948) The estimation of the complement and the titration of the antigen were described by Price (1949, 1950*a*) Cannefax (1949) considered the maintenance of stable control sera Pooled sheep's cells were used for complement fixation tests by Muraschi and Tompkins (1949)

An improved antigen for the Kolmer test was described by Kolmer and Lynch (1948) The Ford-Robertson and Colquhoun modifications of the Meinicke test received attention from Lane (1948), and from McMenemey and Whitehead (1949) Another flocculation procedure, Migliano's test, was described from Brazil by Rangel (1950)

The Price precipitation test was discussed by Price (1948), the Laughlen by Sandiford and Khal (1948), and the Berger test by Douglas (1947) A verification antigen prepared from dried powdered pregnant uterus, fœtus, cord and placenta was described by Hecht (1947) The use of a mechanical pipette for the Kahn test was described by Singh (1949) and a rack for precipitation tests by Price (1949*a*) A rapid method of performing quantitative tests on a slide was reported by Harris and Bossak (1951)

The Chediak test, for which dried blood is used on filter paper which is then allowed to float on saline, and on which a slide test is then performed with Meinicke antigen, was described by Chediak (1948), by Sikorski (1948), and by Harris *et al* (1952*a*) This test was used on 113,845 specimens in Poland by Milgrom (1948) A modified Chediak test, the Citochol test, was described by Hoschek (1949), Heinke and Hoschek (1949) and Fischer (1950) A rapidly performed slide test, applicable to whole blood serum or cerebrospinal fluid, was described by Roemer and Greulich (1949)

Hogan and Busch (1950) described

when only small qua

(1951), Harris *et al*

the Filter Paper Microscopic test but found it less reactive than other tests A simple coloured slide test was described by Hsiang (1947) The micro-reaction of Etcheverry and Marchissio was discussed by Reynault (1948, 1949) and another slide test by von Boros (1949), and by Koehn

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(4) False positive serum reactions

False positive reactions were discussed by Vissian (1947), von Pein

cent of the total number of positive results obtained

There are a number of theories as to the cause of false positive reactions and it is likely that several factors may operate Widelock *et al* (1950) demonstrated the presence of acetone soluble substances in sera which reacted to acetone soluble antigens and speculated as to whether these

serum tests for
between false
relation to the
was there any

ise of false
949) who
or that it
Paoletti
given by

injection, to determine whether minute quantities left in the syringe could produce false positive readings to the Wassermann test Arsphenamines, sulphonamides and lecithin produced false positive results in all sera tested

Wheeler *et al* (1947) showed how the sensitivity of the Kahn test could be increased by the addition of lecithin and reduced by adding cephalin, while Saint Prix and Mutermilch (1949) achieved this with the aid of camphor Lubitz (1946) demonstrated that, whereas Kahn positive syphilitic sera maintained or only slightly lost their titres when kept in an ice box for 2–6 months, all of 109 sera giving false positive results gave negative results, or underwent a reduction in titre, when subjected to such treatment

False negative reactions due to the prozone phenomenon, which may cause negative qualitative but positive quantitative reactions, were described by Beelar *et al* (1949)

Kahn has pointed out that with intentional divergence from standard techniques such as by varying the salt concentration, some degree of seropositivity could be obtained from almost any serum He suggested that a state of 'universal positive' existed which increased in syphilitic persons, the diagnostic threshold being occasionally crossed to produce

false positive readings in non-syphilitic persons Kahn and his co workers studied this phenomenon in a number of diseases which give true and

syphilis, yaws, and pinta, but different in malaria and tuberculosis

The serology of five patients with lepromatous leprosy and histories of syphilis were studied by Pinto and Zeo (1951) Following antisyphilitic treatment there was a reversal to the pattern of lepromatous leprosy Singh (1949) studied the false positive reactions in leprosy and considered that higher titres were obtained in lepers than in sufferers from malaria,

False positive reactions due to malaria do not persist for long after the cessation of clinical activity In untreated cases they last for about two months and in treated cases for one month (Nelson, 1947) Kent *et al* (1948) performed 51,223 tests, employing eight different methods, on 6,403 sera of 104 male prisoners infected with malaria Seventy five showed one or more positive results to one or more of the tests these were found 0–39 days (average 8 7) after parasitæmia and they persisted for 2 181 days

Rosenthal and Widelock (1948) tested 133 patients 7–39 days following smallpox vaccination Twelve showed some abnormality to the Mazzini, Kahn, Kolmer or V D R L slide tests, but in all but one instance these findings were negative when repeated Perrot (1948) tested 390 sera 13 days after vaccination and found some degree of positivity in 55 Tompkins (1949) likewise tested for syphilis the sera of 23 persons who had been vaccinated two weeks previously Five false positive results were obtained in tube precipitation tests with lipoidal antigens, four in slide precipitation

vaccination

Aron *et al* (1952) considered false positive tests in infants, their relation to early congenital syphilis, and the passive transfer of reagin from the mother Vogelsang and Aanje (1949) found 11 false positives in patients with pneumonia Clark *et al* (1951) noted false positive Kolmer tests in 6 6 per cent of 102 patients with Q fever, usually in the second to sixth week

tests for syphilis in 83 cases of disseminated lupus erythematosus, in 20 per cent of 75 cases of periarteritis nodosa, in 7·7 per cent of 348 cases of rheumatoid arthritis, and in 9 3 per cent of 266 cases of rheumatic fever. There were none in 15 cases of dermatomyositis nor in 14 cases of scleroderma

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(5) Treponemal Immobilization test

Nelson (1948) studied the physical and chemical conditions which affect the survival of *T pallidum* in the laboratory Nelson and Mayer (1949) then described a new fundamental of great importance in serological diagnosis of syphilis They showed that the serum of syphilitic rabbits contains an antibody which, in the presence of complement, immobilizes and probably kills *T pallidum* Organisms extracted from rabbit syphilo mas were suspended in a special medium and incubated with complement and the serum to be tested If syphilitic serum was used the treponemes became non motile and lost their power to infect other rabbits.

Magnuson and Thompson (1949) performed the Nelson test on the sera of 362 patients with syphilis, 81 suffering from diseases other than syphilis, 73 normal persons and 91 normal rabbits No positive results

suffering from disease other than syphilis, except in cases of yaws Of 30 patients with primary syphilis 23 showed definite, and four doubtful activity Activity was invariably found in the secondary and later stages

the spinal fluid
f 25 fluids from
lso noted in the
serum reactions

to standard tests, but none was found in 12 patients selected as having false positive serum reactions There appeared to be some decrease in immobilizing activity 6–12 months after the treatment of early syphilis with penicillin, but not after the treatment of late syphilis

This Treponemal Immobilization (T.P.I) test, apart from what it may teach us concerning the course of syphilis is of considerable practical value in the differentiation of false positive and false negative serum reactions Mohr *et al* (1950) applied the test to patients in private practice Of 126 persons with treated late syphilis, 111 of whom were still sero positive, 96 8 per cent proved positive Of the sera of 67 patients suffering from suspected latent syphilis 76 3 per cent were positive while of 63

s, con
er cent

The use of the T P I test in France was reported by Vaisman and Hamelin (1951), and by Durel

tatively by measuring the serum
t of the treponemes after 18 hours

could be induced in mice by the inoculation of a sufficient number of Mapharsen-killed or heat-killed spirochætes of the Nichols strain Khan *et al* (1951) demonstrated that there was cross-reactivity to the T P I test between *T pallidum*, *T pertenue* and *T cuniculi*

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C. SKIN TESTS

Luotest

Skin tests for syphilis, with material from rabbit syphilomas, have not

them further Now that immobilizing antibodies have been discovered, the presence of which may sometimes be detected by the *treponemal* immobilization test in the absence of a positive serum test performed by conventional methods, a further investigation of these skin tests is neces-

as an intradermal test for syphilis on 120 patients The test was repeated on the sixth day if doubtful readings were recorded Positive results were obtained in 54 patients, most of whom were proved to have late syphilis In Great Britain, Csonka (1950) also investigated the test Of 33 cases of

early syphilis, 22 with a positive Wassermann reaction, only two were *positive to the skin test* as were two of 23 controls, both of whom were shown to have previously unsuspected positive Wassermann reactions The test was also positive in 16 of 25 cases of latent syphilis with positive Wassermann reactions, in 15 of 23 Wassermann positive cases of late be-

3 of 26 cases

Twenty four

Seeberg (1951) employed the Luotest at six day intervals on 28 children with congenital syphilis Twenty four showed increased sensitivity to the second test, two failed to respond and two responded only to the third test Marshak and Rothman (1951), using material from rabbit syphilomas, noted positive skin tests in patients with congenital or acquired late syphilis but not in those with primary or secondary syphilis

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D CEREBROSPINAL FLUID TESTS

Spinal fluid from 400 cases was examined at two laboratories and Ford *et al* (1951) reported considerable discord in the findings The effects of contamination with blood on cerebrospinal fluid findings were discussed by Putkonen and Kajanne (1951)

Simultaneous lumbar and cisternal punctures were performed on 102 patients by Davis *et al* (1951) There were few differences as to cell count except in the presence of pleocytosis when the lumbar fluid had the higher count Reactivity to the mastic test and total protein concentration were greater in the lumbar fluid Cecil and Johnwick (1951), in a review of 44 711 diagnostic cisternal punctures performed over five years reported four deaths attributable to the procedure and did not believe there was any justification for the retention of this method of obtaining spinal fluid

Harding and Harris (1949) described a technique in which a photo-electric colorimeter was used with trichloro acetic acid instead of sulpho-salicylic acid as a precipitant, for estimating the protein content of cerebrospinal fluid The use of the zinc sulphate method for precipitating protein was described by Donovan *et al* (1951) Following comparative tests by different methods, that with the photo electric colorimeter was considered the best practical procedure by Gross (1951) Waldman *et al* (1950) *described a method of estimating* protein in small samples

Simplified techniques for the performance of the Lange test were described by Lange *et al* (1950) Victor and Hunter (1949) compared the

results of the Kolmer and V D R L. slide test on the spinal fluid, and Heinke (1951) reported on the use of a micro-flocculation modification of the Chediak test Cannefax *et al* (1949) showed that the results of the Kolmer test on mailed specimens were the more reliable the sooner they were received at the laboratory Mailed specimens usually had a higher protein content than those taken on the spot The Kolmer complement fixation reaction and the V D R L flocculation reaction of the spinal fluid were compared by Cannefax and Beyer (1952)

Wright *et al.* (1951) estimated penicillin levels on 198 samples of spinal fluid taken at varying intervals after commencing a course of 600,000 units of P A M daily In 82 per cent penicillin was present at 31 hours, and in 91 per cent at 122 hours.

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CHAPTER VIII

EARLY SYPHILIS

A. GENERAL

are shown in Figs 6 and 7

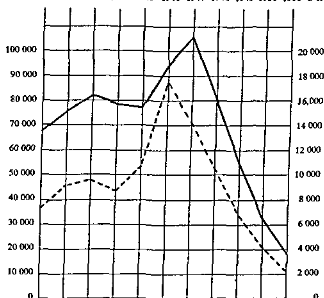


FIG. 6—TRENDS IN THE INCIDENCE OF EARLY SYPHILIS IN THE CONTINENTAL U S A AND ENGLAND AND WALES

U K fall from 1946 peak = 87 1°₀ in 5 years

FIGURES FROM WHICH GRAPH IS COMPILED

	U S A	U K		U S A	U K		U S A	U K
1941	67,958	7,332	1945	77,007	10,746	1949	54,268	6,812
1942	75,704	9 046	1946	94 957	17,675	1950	32,250	4,143
1943	82,230	9,642	1947	106,594	14,166	1951	18,211	2,272
1944	78,418	8,778	1948	80,528	10,637			

Similar falls in incidence have occurred previously following war time peaks, but never before has the drop been so rapid The reason for the precipitate decline must lie either in the case finding mechanisms, or in the drugs used in its treatment or prophylaxis That it is not the case finding which is responsible is evident from the graph, as the decline is just as pronounced in England and Wales, where there is no elaborate case finding machinery, as in the U S A, where case finding efforts are often intense and always considerable

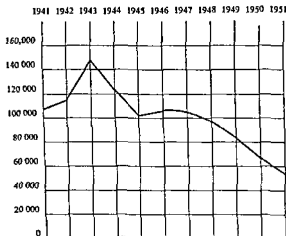


FIG 7—TREND IN INCIDENCE OF EARLY LATENT SYPHILIS IN CONTINENTAL U S A

(*No comparable figures are available for England and Wales*)

Fall from 1943 peak = 64 8% in 8 years

FIGURES FROM WHICH GRAPH IS COMPILED

1941	108 658	1945	101 135	1949	84 342
1942	116 433	1946	107 336	1950	65 567
1943	148 909	1947	107 755	1951	52 309
1944	122,390	1948	97 745		

The most important factor is undoubtedly penicillin It is possible that penicillin given, usually unwittingly, in the incubation period of syphilis has been more responsible for the rapid decline than when the drug has

reduced the risk of contracting it approaches or drops below this limit

From the steep, so far unbroken, fall in incidence it would seem likely that within a year or two early syphilis will be under control, from the

public health point of view, in the well developed countries Like diphtheria the disease will have become a rarity within a lifetime There will still be some imported cases, however, and control measures will have to be concentrated on the ports

TABLE 5

CASES OF ACQUIRED SYPHILIS WITH INFECTIONS OF LESS THAN ONE YEAR TREATED IN THE CLINICS OF ENGLAND AND WALES

(Ministry of Health figures)

Year	Male	Female	Total
1931	6 421	2 683	9 104
1932	6 196	2 532	8 728
1933	5 949	2 141	8 090
1934	4 888	2 030	6 918
1935	4 226	1 745	5 971
1936	4 033	1 642	5 675
1937	3 986	1 647	5 633
1938	3 744	1 494	5 238
1939	3 574	1 412	4 986
1940	4 029	1 582	5 611
1941	5 023	2 309	7 332
1942	5 470	3 576	9 046
1943	5 159	4 483	9 642
1944	4 384	4 934	9 318
1945	5 214	5 577	10 741
1946	10 705	6 970	17 675
1947	8 750	5 416	14 166
1948	6 603	4 034	10 637
1949	4 392	2 470	6 812
1950	2 678	1 465	4 143
1951	1 498	774	2 272

B CLINICAL

Kuhl and Boggs (1948) found that the lesions of seronegative primary syphilis were multiple in 43 2 per cent of 190 cases The well known explanation of the fact that chancres are less commonly seen in women than in men is that they may be sited on the cervix Six cases of cervical chancre were reported by Ferrari (1947) Vaginal chancres are uncommon but one was reported by Putkonen (1951)

Fowler (1948) noted a regional adenitis with 73 per cent of 18 chancres present 1–3 days, 78 per cent of 41 chancres present for 4 6 days and [illegible]

means

So called syphilitic balanitis and vulvo vaginitis were considered by Follmann and Gougerot (1948), and by Navarro Martin (1950) Pasini (1948) recovered *T pallidum* from the tonsil in 8 of 25 cases of seronegative

primary syphilis, and in 7 of 16 cases of seropositive primary syphilis The limitations of the dark field technique in the differentiation of oral spirochætes requires no stress

Martin (1947) denied the significance of enlarged epitrochlear glands as a diagnostic sign of secondary syphilis, finding such enlargement in 42 per cent of 200 normal soldiers Willcox (1949) reported enlarged epitrochlear glands in 26 of 100 normal African soldiers, and in 54 per cent of 100 African labourers examined in Southern Rhodesia

A condition of the scalp called *witkop* which affects the Negroes of parts of South Africa and resembles favus, was described by Marshall

syphilis were described by Thompson and Preston (1952)

Kuhl and Sauer (1949) analysed 1,732 case records of patients with secondary syphilis and found 29 in which supposedly negative serum tests had been obtained When these cases were critically examined not one negative result of a properly conducted test was noted

The white cell counts of 405 cases of early syphilis were analysed by Willcox (1948), who could detect in the findings no striking distinctions between seronegative primary, seropositive primary and secondary syphilis The same author (1948*a*) studied the effects of ten daily injections

TABLE 6

EFFECTS OF ARSENOXIDE ON THE WHITE CELL COUNTS OF 405 CASES OF EARLY SYPHILIS

(given as ten daily injections of 0 06 g)

	Average count before treatment	Average count after treatment
Polymorphonuclears	5 560 (62 0%)	4 505 (59 0%)
Lymphocytes	2 830 (31 5%)	2 590 (34 0%)
Large mononuclears	410 (4 5%)	375 (5 0%)
Eosinophils	125 (1 5%)	120 (1 5%)
Basophils	25 (0 5%)	30 (0 5%)
Total	8 950	7 620

mononuclears also (Table 6)

The electrocardiogram in 40 cases of early syphilis was studied by

Steiger and Edeiken (1948) who discovered abnormalities in the T waves, and in some cases RS-T changes as well, in 42 5 per cent

test) in approximately 5 per cent—the amount and degree of abnormality varying with the stage of syphilis

References

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African in Southern Rhodesia, p 24, Southern Rhodesia Govt

C. TRANSMISSION OF SYPHILIS

Of 219 patients with *extragenital chancres*, seen over a period of 34 years at the Johns Hopkins Hospital, Baltimore, Tucker and Mulherin (1948) reported that 52 per cent had lip lesions Murrell and Gray (1947) recorded

–8½ years,

e reported

were seen

In the latter cases overcrowding was believed to have been the cause An increase in the incidence of syphilis of this kind under deteriorating social conditions was also reported from post war Budapest by Fejer (1948), who stated that in the years 1937–1939 only three such examples

The theory of *seminal transmission* was agun revived by Ross (1948) to explain infection of the consorts of two patients with treated syphilis five months and three years respectively after seronegativity had been reached Golay (1946) concluded that the paternal transmission of syphilis, while not proved, was at least possible if the spirochæte assumed an ultramicroscopic form

A case of *transfusion syphilis* was reported by Mayne (1947) According to Lohe (1948) such transmission occurs about once in 4,000 blood transfusions Idsøe (1951) reported a case in which a father may have given syphilis by blood transfusion to his daughter—the event not being discovered for four years Bernard (1947), however, recorded a case to show that even if syphilitic blood is used for transfusion purposes the

processing by deep freezing and drying Bessemans and Derom (1946) affirmed that 'Chinosol added to whole blood before transfusion would prevent transfusion syphilis, and Bessemans *et al* (1951) reported that calcium ortho oxyquinoline, when added to blood, killed the spirochætes within twenty minutes Schwalm (1951) transfused three persons with blood from a secondary syphilitic treated in his way Probey (1951) tested the sterilizing powers of ultraviolet light against infective rabbits' blood Whole blood exposed for 0 52 sec remained infective whereas plasma exposed for 0 25 sec did not

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D. TREATMENT OF EARLY SYPHILIS

(1) Metallotherapy

(a) General

that used to be necessary However, the fact that a much larger number of patients defaulted before this time, compared with virtually none when penicillin is used, means that the latter is without doubt the drug of choice

James *et al* (1948) analysed the material from the Central Syphilis

reported only nine failures, four of which were considered to have been reinfections Thompson and Smith (1950) reviewed the results obtained in the treatment, with metallotherapy, of 771 patients with early syphilis during the years 1921–1933 After a follow up of 16–29 years no less than 90 4 per cent of those who originally completed two or more courses of treatment were cured

Burckhardt (1949) followed up 475 cases of early syphilis treated with neoarsphenamine and bismuth during the years 1932–1937 A consider able number reacted unfavourably to the treatment and there were five deaths *No less than 90 per cent showed no clinical or serological evidence*

Pillsbury and Loveman (1947) employed an intensive schedule of 20 daily injections of arsenoxide to a total dose of 20 mg per kilo together with a total of 1,280 mg of metallic bismuth as eight injections of the sub salicylate in oil Out of 1,343 patients followed up for one year there was 4 26 per cent of relapses Only six abnormal spinal fluids were noted in 785 examined Although there was no fatality in 4,000 patients treated the course was considered too toxic

Using the Eagle 12 week schedule, with 40 injections of Mapharsen and ten of bismuth, Weiner (1947) reported 4,800 cases treated without a death, *but only 54 per cent of patients actually completed treatment* Of 175 cases of early syphilis followed up for six months or more a satis factory outcome was noted in 141 Of 2,842 patients followed up out of 3,000 treated in the U S Army with a 26 week schedule of 40 injections of Mapharsen and 16 of bismuth, reported by Sternberg and Leifer (1947), a satisfactory outcome was noted in 95 36 per cent of the 87 per cent observed nine months or more Of 2 842 patients tested in this series abnormal spinal fluid was noted after treatment in only 0 64 per cent

Dexter (1947) reported success in 95 5 per cent of 110 early cases of syphilis treated with 30 injections of Mapharsen and 10 of bismuth given over 9-15 weeks

Beerman and Wammock (1947) tried both the 12- and 26-week schedules with dichlorophenarsine hydrochloride They considered that this substance was no more toxic than Mapharsen

Heller (1946) reviewed the results of rapid treatment of secondary syphilis with arsenic alone, arsenic and bismuth, and penicillin alone, or in combination He reported that the 5 day intravenous drip with ... the best results but was also the most toxic Although

lin and

mbined

treatment had any advantage over penicillin alone Similar findings were reported in Britain (Willcox, 1947) The uses and abuses of chemotherapy were also considered by Lees (1951) and by Laird (1951)

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(b) Toxic effects of arsenic

It was the toxic effects of arsenic which finally led virtually to its ...

In general the arsenoxides were less toxic than the arsphenamines Burton *et al* (1946), for example, reported 25 mild and 13 severe reactions with one death in 108,922 injections of Mapharsen in the U S Navy, compared with one mild and three severe reactions with one death in only 2,030 injections of neoarsphenamine

That fatalities are occasionally due to arsenical treatment was emphasized by Pirila (1949), who reported 11 deaths in 385 cases of syphilis treated in

Finland during a period of 25 years All who died had dermatitis, four with liver damage and four with encephalopathy in addition Such incidents may now be avoided if penicillin alone is used

Cormia and Blauner (1947) recorded the toxic effects in a series of 500 patients treated on a 20-day arsenoxide regime Ninety five per cent com pleted treatment although some interruptions were necessary in 157 There were two cases of arsenical encephalitis, 14 of cerebral irritation, three of agranulocytosis and six of jaundice (the latter usually arising about the 16th day) Kurth (1950) reported a case of arsenical dermatitis associated with anhidrosis and believed that the latter condition arose as a result of the effect of arsenic on the diencephalon Parnitzke and Dohner (1950) noted an increase in the neurological complications of polyneuritis encephalitis and myelitis following the arsenical treatment of early syphilis in Halle Twenty five cases of arsenical agranulocytosis were described by Schoog (1949), and a case of aplastic anæmia by Hart and Humble (1949)

The most severe complication, especially with intensive and semi intensive methods, was arsenical encephalopathy A death during a con servative course was reported by Hipps and Goldberg (1947) Indians are particularly prone to arsenical encephalopathy Prebble (1946) reported 187 such cases, all but two being in Indian patients treated with modest weekly or bi weekly doses of neoarsphenamine He was not particularly impressed by the action of B A L on the encephalopathy

Post treatment jaundice at one time considered to be directly caused by arsenicals, although it usually occurred about 100 days after the onset of

is never far away if sterilization precautions are neglected was indicated by Morton (1948) Malmros *et al* (1948) showed that the condition could follow a mere needle prick for blood sampling

Neering (1948) reported 39 cases of ninth day erythema in 1,100 patients treated Treatment with arsenic was resumed but had to be stopped again in nine one of whom developed agranulocytosis Such a risk which often had to be undertaken in pre penicillin days, is now no longer justifiable *Reymann (1950) considered ninth-day erythema and* encephalopathy to be part of the same syndrome Reymann (1948) believed ninth day erythema to be due to activation of a latent streptococ cal infection by neoarsphenamine

Sexton and Gowdey (1947) discussed the relationship between aneurin and arsenical toxicity They found an increase of sugar and *pyruvic acid* in the blood of patients undergoing intensive arsenical therapy and con

sidered that arsenic should not be given in the presence of vitamin B deficiency For this reason intravenous arsenic was not recommended for pregnant women It was also suggested, in the event of toxicity, that vitamin B should be given in addition to B A L

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(c) B A L

Eagle and Magnuson (1946) reported 227 cases of various forms of [illegible]

these recovered Of those with coma or convulsions, however, who were treated within ½–6 hours of the onset, 20 per cent died When treatment was delayed beyond 24 hours, five out of nine succumbed The drug was considered to have considerable value in 88 cases of arsenical dermatitis Of 11 patients with agranulocytosis, 10 recovered but blood transfusions and pentnucleotide were also given Two of three other patients with aplastic anæmia however died Twelve other cases of agranulocytosis were also reported by Fisher *et al* (1947) All received B A L in addition to other forms of treatment and all recovered In 1947, B A L was the subject of a Medical Research Council Report Of 44 cases of arsenical dermatitis treated by Carleton *et al* (1948) with B A L the response was good in 23, fairly good in 8 and doubtful in 7 There was no response in 3 and 3 patients died A case of arsenical purpura, successfully treated with B A L, was reported by Kahrs (1947)

It was somewhat ironic that arsenic fell into disuse just as soon as an eff[illegible]

forgo[illegible]

poner[illegible]

of syphilis would remain positive for some days when Mapharsen and B A L were administered simultaneously

Thompson and Whittaker (1947), working with pigeons, found that B A L was also an antidote for mercury, gold and antimony, while Stocken (1947) noted that it prevented mercury poisoning in rats A case of bismuth stomatitis in man successfully treated with B A L was reported by Reekie (1949)

Holley (1950) recommended the use of Benadryl to combat the minor side-effects of B A L

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420–4

yph Chicago, 55,

41, 342–6

(d) Bismuth

Eagle (1946) contrasted both the toleration and therapeutic properties of bismuth in a watery solution, in an oily solution, and in an oily suspension He found that the order of toleration was the reverse of that named and that, although the curative effects did not widely differ, the oil soluble

muth no innocuous substance, for of 143 patients receiving a minimum of three courses of the drug 33 developed severe stomatitis and 37 showed urinary abnormalities

The practice of giving bismuth alone for the treatment of syphilis was retained in some parts of France for longer than elsewhere At a conference held in 1946 Lortat Jacob reported 150 cases given 40 injections of oil-soluble bismuth over a period of 17 weeks Serum reactions became

bismuth in addition to the week of treatment with penicillin Later, because the occasional severe toxic reactions following the arsenic were still encountered, arsenicals were abandoned, and after the daily penicillin course

only bismuth was given weekly for ten weeks More recently still, with cases of bismuth stomatitis still occurring, many British clinics have abandoned bismuth also After the eight-day course of penicillin, ten weekly or bi-weekly additional injections of penicillin alone have been given in the belief that there is nothing that an injection of neoarsphenamine and/or bismuth can do which penicillin cannot do better and more safely

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with four fever sessions induced by T A B vaccine The results were disappointing

Rodriquez *et al* (1949) reported 568 cases treated with eight hours of fever by hypertherm, plus Mapharsen in doses up to 1 76 mg per kilo, with 150 mg of elemental bismuth before fever There were 167 failures Of 137 others given fever, Mapharsen and bismuth over a 30 hour period the failure rate was 13 per cent at 12–15 months

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(2) Penicillin therapy

(a) General

The work of Duchesne, who in 1897 showed that *B coli* and *Salmonella typhi* could, when mixed with *Penicillium*, be injected intraperitoneally with impunity, was recalled by Justin Godart (1949)

The electron microscope was used in the study of the actions of penicillin, streptomycin and other antibiotics by Babudieri (1948)

Some cases of syphilis *can* occasionally be cured by very small doses of pe[illegible]
se[illegible]
re[illegible]

[illegible] penicillin by intravenous drip over 24 hours Bundeson *et al.*

(1947) had previously reported 61 failures out of 129 patients given 10 million units by this method

Hasselmann (1949) presented the results of 370 cases of early syphilis treated with penicillin in conventional dosage Soviet penicillin was used on 134 cases by Arutyunov *et al* (1948) The treatment of early syphilis with penicillin was discussed by McElligott (1948), and the results by race and sex of the penicillin treatment of syphilis were given by Bauer and Price (1949)

Moore (1948) presented co operative data from American clinics and made the general statement that, with 1 2–9 6 million units of penicillin alone given over 4–15 days, the failure rate at 2 years was in the region of 25–35 per cent Most of the failures were of the 'relapse reinfection' group, it being impossible to tell for certain which was which The rapid cures obtained with penicillin have permitted reinfections to occur at a frequency unheard of with the older more prolonged methods of treatment (see Experimental syphilis, p 63) Moreover, these results were obtained with commercial penicillin, and better figures might be anticipated with the employment of crystalline penicillin G

Health Service in the 'Blue Star' series of patients selected for ease of follow up After two years of observation of 1,538 patients treated by various penicillin schedules, 92 3 per cent of those initially with sero

Iskrant *et al* (1951), and the follow-up methods which achieved 90 per

14,255 with seropositive primary syphilis only 7,380 (51 8 per cent) became seronegative, whereas 33 7 per cent remained seropositive and 14 5 per cent suffered a serological relapse Of those remaining seropositive at a low titre 12 9 per cent showed clinical relapses, but of those with a persistent high titre as many as 30 per cent relapsed clinically Seroresistance following the treatment of secondary syphilis was considered by Thomas *et al* (1952)

In a statement made by the Syphilis Study Section of the United States Public Health Service in 1948, a minimum total dose of 4 8 mega units of penicillin given over 8 days was recommended for early syphilis

The serological response to penicillin therapy, as judged by the alterations in the quantitative Kahn Test, was studied by Clark *et al* (1947) In general the response was similar to that obtained with treatment with arsenic and bismuth although it was not quite so marked in the case of secondary syphilis

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[illegible]

(b) Aqueous penicillin

With minute doses of 60 000–600,000 units of aqueous penicillin Maillard and Orzel (1946) reported a failure rate of 85 per cent With total doses as low as 600,000 units given over 7½ days the failure rate has also been high Bauer *et al* (1947) had 97 failures in 339 patients so treated, while 14 of 34 cases reported by Smith *et al* (1947) were not cured

Mahoney *et al* (1949) reported on the first four patients ever to be treated with penicillin (1 2 mega units) after a follow-up of 6 years One had been retreated

Bundeson *et al* (1949) stated that of 639 patients given 2 4 mega units of commercial penicillin over 7½ days, of whom 369 were observed for 360 days or more [illegible]

9 months or more, a successful outcome being claimed in 83–94 3 per cent. Arnold *et al* (1947) reported only 17 failures in 728 patients, half of whom were observed for 183 days or more, treated with 85 2-hourly injections of 40,000 units to a total of 3 4 mega units The discrepancies between the latter findings and the Co-operative American material, which Moore (1948) stated showed an over all retreatment rate of 25–35 per cent at 2 years, were the subject of a special study by Reynolds (1948), who found that the Co operative cases contained a high percentage of Negro females whereas Arnold's series had a preponderance of white seamen in whom the possibility of reinfection was less Lees and Watt (1950) noted only seven relapses or reinfections after a follow up of 2 years in 123 cases of early syphilis treated with 2·4–4 8 mega units of penicillin in the British Armed Forces Blackwood *et al* (1948) gave 4 8 mega units in 2-hourly injections over 7½ days and had a cumulative failure rate of 17 per cent at 11 months This was no better than if 1 2 or 2 4 mega units had been given over the same time

The fact that penicillin G proved more effective in the treatment of rabbit syphilis than the other fractions F, X and K, both as to the cures obtained (Carpenter *et al* (1946), Arnold *et al* (1947*a*)), and also as to the rate of disappearance of spirochætes from the lesions (Olansky and Putnam (1946), Turner *et al* (1947)), led to the manufacture of purer penicillin in terms of G Crystalline penicillin G came on the American market in the summer of 1946 Schwemlein *et al* (1950) compared the results obtained by crystalline and commercial penicillins on a schedule consisting of 2 4 mega units given over 7½ days At 12–15 months there was a failure rate of 15 6 per cent with crystalline penicillin compared with 24 4 per cent with amorphous penicillin

Rider (1949), in an analysis of co operative results, found that those obtained with crystalline penicillin G were the best, although there was no significant difference whether the penicillin was given every two or three hours, or in a dosage of 2 4 or 4 8 mega units, over a period of eight days Plotke *et al* (1951) reported 228 cases treated with 4 8 mega units of crystalline penicillin G over 7½ days The cumulative failure rate at 15 months was 13 7 per cent, and they also believed that little was to be gained by increasing the dose from 2 4 to 4 8 mega units

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(c) Penicillin in oil-wax

Penicillin in oil beeswax was the first of the repository penicillins Evolved by Romansky and Rittman (1945) the preparation (so called Romansky formula) contained 300,000 units of high-potency calcium penicillin per 1 ml of arachis oil with 4 8 per cent w/v sunbleached beeswax After an intramuscular injection of 300,000 units, penicillin was detectable in the serum for 18 or more hours, and after an injection of 600,000 units penicillin would remain in the serum for a minimum of 24 hours

Thus single daily injections on an ambulatory basis came to replace repeated injections of aqueous solutions and enjoyed world wide usage for the treatment of syphilis The principal disadvantage of oil-beeswax penicillins was that they tended sometimes to stick in the syringe and required warming before use They have now been superseded by procaine penicillin preparations which are not only more efficient but easier to administer

Thomas *et al* (1947) reported very good results in 802 cases treated with eight daily injections of 600,000 units of penicillin in oil wax and stated that there was no extra advantage in giving the injections twice a da[illegible]

150,000 units of penicillin in oil-beeswax given twice a day for 10 days

Rauschkolb and Cole (1949) treated 175 cases of early syphilis with eight daily injections of 600,000 units of oil wax penicillin Of the 57 cases of secondary syphilis, however, 17 became seronegative within 10 months, 19 remained seropositive and no less than 21 relapsed

On the other hand, Bowden and Holmes (1950) claimed only a 10 per

cent failure rate on a regime whereby 600,000 units of penicillin in oil wax was given daily for 6 days Chargin *et al* (1949) reported a series of 199 cases given the same dose of oil-wax penicillin daily for 10 days Of the

up for 4–9 months Previously this author (1947) had reported that of 529 cases followed up for 9 months or more, out of 802 given eight daily injections of 600,000 units of penicillin in oil beeswax, there was a success rate of 85 1 per cent Heyman (1948) had 21 1 per cent of failures in 53 patients given ten daily injections of 600,000 units This compared with a failure rate of 17 1 per cent in 23 patients given 600,000 units twice weekly for 8 weeks

The great advantage of ambulatory penicillin schedules is that almost all patients receive a minimal curative dose without defaulting Hayman and Aitken (1947) reported that all of 107 patients treated with penicillin in oil-wax attended long enough to be given a minimum curative dose while, of 437 patients treated by Chope and Malcolm (1948), 96 6 per cent completed treatment, compared with 26 6 per cent with the old long-term arsenic and bismuth schedules

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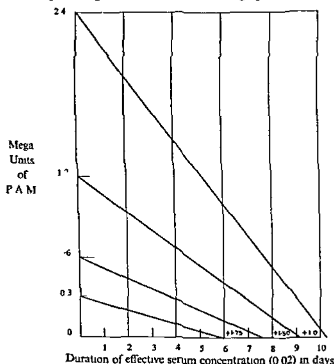
(d) Procaine penicillin with aluminium monostearate (P.A.M.)

The discovery that penicillin G will combine with procaine in equimolecular amounts to form procaine penicillin, with the use of which serum

its
nt

aluminium monostearate This substance is now generally used as a standard for the treatment of syphilis, whatever the schedule, all over the world It is relatively easy to administer and can even be given by 'jet' injection (Weiner *et al*, 1952)

Thomas *et al* (1948) were able to detect penicillin in the blood for 96 hours following the intramuscular injection of only 300,000 units of P A M, and found that a detectable level persisted for a longer period with a fine particle penicillin than with a large particle penicillin Several



Duration of effective serum concentration (0 02) in days

FIG 8—P A.M LAW OF DIMINISHING RETURNS

(Figure by courtesy of Venereal Diseases Division, World Health Organization)

authors (e g Young *et al* (1949)) showed that, after single intramuscular injections of 2 0–2 4 mega units of P A M, penicillin was detectable in

P A M a level of economic efficiency *in the dosage In the same way as* the power of a ship has, once a given point is reached, to be increased disproportionately to the resultant increase of speed produced, thus as the individual dose of P A M is increased, the so-called 'law of diminishing returns' does not permit a proportionate increase in the duration of the blood level of penicillin

Thomas (1948) recommended three experimental schedules for P A M

o

e

lost to observation 17 had been insufficiently followed up but there were only three known failures in the remainder

By 1950 Thomas *et al* reported on 72 patients followed up for 6–20 months after receiving single injections of 1 2 or 2 4 mega units and on 135 patients treated by the other two schedules Of 24 receiving single doses of 2 4 mega units there was one relapse one reinfection and one case of seroresistance The results were not appreciably better than those in 48 patients receiving only 1 2 mega units This series was reported on again by Thomas *et al* (1951) By this time 68 cases of secondary syphilis had been treated by single shot methods

Wright *et al* (1950) treated 123 patients with early syphilis with a single dose of only 300 000 units with a failure rate at one year of 19 per cent When 600 000 units were given once daily for 3 days the failure rate at 21 months was 11 5 per cent

Taggart *et al* (1949) treated 97 patients with P A M and of 25 given single injections of 1 2 3 0 mega units and followed up for 6 months only two required retreatment Alexander *et al* (1950) had a 20 2 per cent failure rate at one year in 109 patients given 1 2 mega units and only 12 2 per

A furthe

P A M

by Rangiah (1950)

Parkhurst *et al* (1952) reported on 60 patients with secondary syphilis given a single injection of 2 4 mega units of P A M At follow up after 12 15 months there were 8 2 per cent of failures and 3 6 per cent of rein fections Of 86 others given two injections of 1 2 mega units at intervals of 96 hours and followed up for the same time there were 8 0 per cent of failures and 2 5 per cent of reinfections

Jones and Heyman (1952) treated 103 cases of early syphilis with 1–4 injections of P A M A single injection of 1 2 mega units was found to be insufficient there being 15 failures in 29 treated The other schedules produced results comparable to those obtained by larger dosages of repository penicillin administered at shorter intervals

Consolidated American data now suggest that single shot treatments with P A M are as effective as when the same total doses are given in

et al

Health

onths

at only 10 per cent

(1950) ... 75 ... of ... yaws

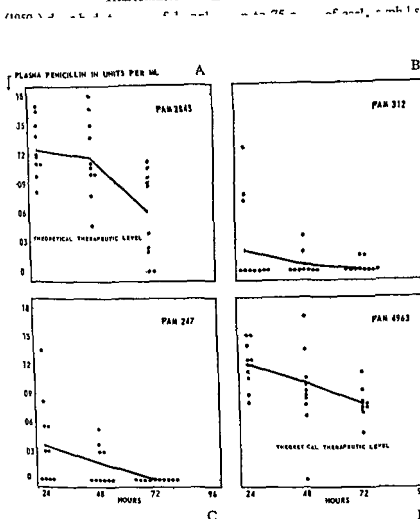


FIG 9—PLASMA PENICILLIN CONCENTRATIONS (SARCINA LUTEA TECHNIQUE) FOLLOWING INTRAMUSCULAR INJECTION OF 300 000 UNITS OF PROCAINE PENICILLIN IN OIL WITH ALUMINIUM MONOSTEARATE (P A M) OF DIFFERENT MANUFACTURE

(*a*) and (*d*) show adequate levels (*c*) an indifferent level and (*b*) a bad level
(*Based on a chart obtained from the World Health Organization*)

success for all cases of penile sore in the African in areas where no facilities for dark field diagnosis existed

When a single or a few injections of P A M are used to cure syphilis (or yaws) it is essential that the penicillin preparations used be up to standard Guthe *et al* (1952), in a paper read at the Tenth International

Congres

P A M

World H

P A M preparations and these are being embodied in the International Pharmacopœia (see Table 7) The most important is that penicillin must be found in the blood (*Sarcina lutea* technique) of the majority of subjects

many batches of P A M have to be tested

In general P A M has been applied dose for dose to those schedules in which penicillin in oil beeswax was formerly employed Eight daily injections of 600,000 units of P A M are commonly given In an attempt to evolve a penicillin schedule satisfactory to the individual, and yet at the same time enjoying the benefit of the extraordinary properties of

C

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four days

TABLE 7

W H O SPECIFICATIONS FOR PENICILLIN PROCAINE G IN OIL WITH ALUMINIUM MONOSTEARATE

Description

Specifications

2 *Procaine penicillin G in oil with 2 per cent w/v aluminium monostearate*

(*a*) *Potency, sterility moisture and packaging* Must conform to the requirements given in the attached Schedule 2

(*b*) *Penicillin particle size* At least 65 per cent of the particles must be 5 microns or less as determined by microscopic chamber counts

(*c*) *Stability* The product should represent a stable emulsion When shaken by

(*d*)

(*e*) *Syringeability* The product must be readily withdrawable and injectable through an 18 gauge needle

(*f*) *Blood concentration* The injection of one ml (300 000 units) intramuscularly into humans should maintain a penicillin blood concentration of not less than 0 03 unit/ml for 72 hours after injection in the majority of subjects (*Sarcina lutea* technique)

SCHEDULE I

Requirements for

Potency, moisture sterility, toxicity, pyrogenicity, pH, crystallinity and penicillin G content of Procaine Penicillin G used in compounding Procaine Penicillin G in oil with 2 per cent Aluminium Monostearate

1 Procaine Penicillin G is procaine penicillin which contains not less than 85 per cent by weight of the procaine salt of penicillin G
2 Potency of Procaine Penicillin G must not be less than 900 units per milligram
3 Procaine Penicillin G must be
   (*a*) sterile
   (*b*) non pyrogenic
   (*c*) non toxic
   according to test procedures acceptable to authorized Government authorities
4 The moisture content of Procaine Penicillin G must not exceed 4 2 per cent
5 The pH of saturated aqueous solution of Procaine Penicillin G must not be less than 5 and not more than 7 5
6 Procaine Penicillin G must be crystalline as revealed by examination, when mounted in mineral oil, by means of a polarizing microscope and using criteria acceptable to recognized Government authorities

SCHEDULE II

Requirements for

Potency, sterility, moisture and packaging of Procaine Penicillin G in oil with 2 per cent aluminium monostearate

1 [illegible]
2 The potency must be 300 000 units per millilitre, as determined by assay methods acceptable to recognized Government authorities
3 It must be sterile as determined by methods recognized by Government authorities
4 The moisture content must not exceed 1 4 per cent
5 [illegible] authorities for good practice

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(e) Diamine penicillin

It is likely that the penicillin Bicillin, or others like it, will in time replace all of the current preparations in use for syphilis This penicillin (N,N'-dibenzylethylenediamine penicillin G, or Bicillin, Wyeth) is under trial

weeks, and in some cases for much longer (O'Brien and Smith, 1952)

This penicillin is likely therefore to revolutionize the present treatment schedules and may result in a general acceptance of a short course of

taneously' treated, it is obviously not always feasible to complete such

ments of population groups a reality

Reference

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(f) Unusual penicillin schedules

Lourie (1948) claimed good results in 98 cases treated with two or three injections of penicillin a day at intervals of one hour over five days (7 5–10 mega units), but such schedules are doomed to extinction on account of their inconvenience to the patient

[illegible] there is now no objection to the

patients with 600,000 units of penicillin in oil-wax twice weekly for eight weeks with seven treatment failures Five secondary cases relapsed and four others were still seropositive at a lower titre Sobel *et al* (1950) reported on a schedule whereby 300,000 units of penicillin in oil-wax was given twice weekly for eight weeks Using P A M , Buschemeyer *et al* (1951) reported on 102 patients with early syphilis given only 300,000 units once weekly for four weeks, 85 per cent of these cases were followed up for six months or more and there were 5 3 per cent of relapses

Syphilis may also be cured by penicillin given orally but absorption of drugs from the stomach is less certain than by injection unless wasteful amounts are employed Oral penicillin is indicated for children who fear injections, in which case three to five times the injection dose should be used It also has an occasional place in the treatment of hæmophiliacs Buerk and Tucker (1949) reported the case of a syphilitic hæmophiliac treated with 48 mega units of penicillin given orally

The use of caronamide to delay the excretion of penicillin, and therefore the prolongation of the penicillin blood level, has been discussed by various authors including Zeller *et al* (1949) and Meads *et al* (1948), who gave 2–4 g of caronamide orally every four hours for 12 hours before, and for 24 hours after, the parenteral administration of penicillin

Seeler *et al* (1948) also had good results with caronamide but the response was unsatisfactory if sodium benzoate was used instead Janowitz *et al* (1948) claimed that the use of caronamide might increase the amount of penicillin in the cerebrospinal fluid, and Collins *et al* (1948), employing oral penicillin, reported a small and variable concentration of penicillin in the blood with its use Hunter and Wilson (1948), on the other hand, found a reducing substance appearing in the urine during caronamide administration and considered, therefore, that it should be used with caution

The general adoption of caronamide and other delayed-excretion methods has been rendered unnecessary by the perfection of delayed-absorption techniques

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[illegible]

It therefore seems justifiable to treat the known contacts of infectious syphilitics *before* the development of signs, provided it is explained to the patients that they will have to have the full 2–3 year follow-up with serum and spinal tests just as if the syphilis had really been known to be present This may be said to be fair comment on the present position of syphilis in the individual For syphilis (and yaws) of populations in undeveloped areas the necessity for treating contacts in mass treatment schemes has already been accepted

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(h) Relapses and reinfections

One of the points extracted from the first consolidated American returns concerning commercial penicillin was that a person who had relapsed once after a given dose was more likely than an untreated person to relapse again Rider (1950) later re-examined this thesis, and could find no such

trend in respect of patients treated with crystalline penicillin G As time has advanced opinion in doubtful cases has swung in favour of reinfection rather than relapse Continued reinfection between partners has been aptly called 'ping pong' syphilis The difficult distinction between relapses and reinfections was considered by Schamberg and Steiger (1948), who devised a form of graphic representation

Thomas and Landy (1950), analysing 726 case records of patients requiring retreatment after penicillin, considered that one half of the so-called failures were probably reinfections Similarly, of 137 apparent failures in 1,105 cases of syphilis treated with penicillin by Schoch and Alexander (1949), no less than 80 were considered to be due to reinfection

Schamberg (1950) considered the problem of the differentiation of sero-relapse from seroresistance in patients found to be seropositive after a lapse from surveillance after treatment Individual case reports of patients relapsing after penicillin were presented by Wexler *et al* (1949) and Downing (1950) Peabody and Webster (1949) analysed the so called relapses since the year 1932 Of a series of 140 no less than 76 were considered to be reinfections

Reinfection with syphilis following treatment with penicillin can occur immediately after the cessation of treatment With the older long term schedules, involving weekly injections of arsenic and bismuth not only was a 'sterilizing' injection given regularly for a long period of time, but also the slower cure resulted in an increased immunity (see Experimental syphilis, p 61 *et seq*) to a further infection It has been the impression of clinicians that reinfections were rare during the arsenical era, but they did occur

Thomas and Landy (1951) analysed the case records of 8,000 patients given rapid treatment for early syphilis and found 311 with definite previous hi[illegible] itment in pre penicillin days Two [illegible] patients previously well treated for [illegible] Peabody and Webster (1949) Both cases had been seronegative for some time

Relapses to penicillin in 437 patients were considered by Sackett and Boggs (1949), 12 9 per cent had an abnormal cerebrospinal fluid on first admission, and of 45 tested on relapse, no less than 28 were abnormal, but only in two cases was the fluid reaction more strongly positive than at first

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Scha[illegible]
Scha[illegible]
Scho[illegible] 103
690–700 [illegible] 60,
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(i) Side effects of penicillin

Thomas *et al* (1948) reported no serious reactions in over 10,000 patients

of penicillin therapy and is usually well controlled by antihistaminics (Pillsbury *et al* (1947), Willcox (1946))

McLachlan and Brown (1947) noted menstrual disturbances in 91 3 per cent of 216 non-pregnant women treated with penicillin, and there were other disturbances noted during pregnancy, the puerperium and the menopause As these findings were not substantiated either in the American literature, or in the light of later experience in Britain, it is likely that they were produced by impurities rather than by penicillin itself

Lepper *et al* (1949), in an analysis of 1,303 patients treated with penicillin, found 1 2 per cent of allergic reactions with aqueous crystalline penicillin G, 2 7 per cent with penicillin G in oil wax, and 1 4 per cent with procaine penicillin The incidence of reactions in some patients

possibly resulting from accidental intravenous injection

Volini *et al* (1950) reported a new penicillin O which was given intranasally, orally and parenterally without allergic effects to persons known to be sensitive to penicillin G A substitute for procaine penicillin, 1 2 diphenyl-2-methylamine ethanol penicillin, with anti allergic properties, was described by Kadison *et al* (1951)

A case of almost complete sciatic paralysis following the injection of penicillin in oil into the nerve was described by Tarlov *et al* (1951)

Herxheimer reaction

A solution of aqueous penicillin containing 20,000 units per ml was held under the foreskin of patients with primary syphilis by Cutler *et al* (1951) Signs of a local Herxheimer reaction ensued and *T pallidum* disappeared from dark field specimens, taking 5–6 days to reappear

A febrile Herxheimer reaction was noted in 384 of 939 patients with early syphilis treated in 20 U S clinics by Farmer (1948) Putkonen and Rehtijarvi (1950), in a study of the Herxheimer reaction on 125 patients,
primary stage, was regularly present in
was most intense in late primary and

The morphological changes in microscopical sections of the lesions taken during a Herxheimer reaction were described by Sheldon and Heyman (1949) Sheldon *et al* (1951) found that the histological changes

caused in rabbit syphilomas by the administration of immune serum were in every way similar to the histological pictures produced by penicillin or arsenic A like state of affairs was noted by the same authors (1951*a*) in respect of ratbite fever The occurrence of the Herxheimer reaction is apparently not prevented by the administration of cortisone or ACTH The pathogenesis of the Herxheimer reaction was again reviewed by Heyman *et al* (1952)

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(3) Combined therapy

(a) Penicillin, arsenic and bismuth

When penicillin was first introduced, and when it was less pure and less efficient than it is today, there was a reluctance in Great Britain to accept it as the [illegible]
Forces
of a co [illegible]
arsphenamine, or its equivalent, and 2 0–2 4 g of bismuth, over a period of 8–12 weeks

Eames and Archer (1947) made a study of penicillin blood levels in patients [illegible]

penicillin plus a course of neoarsphenamine and bismuth, and had only 10 failures in the 70 2 per cent followed up for nine months or more Sixty four patients had reactions severe enough to cause the stoppage of the arsenic, and these workers switched to penicillin and bismuth (later to replace the bismuth by more penicillin) Of 744 of these cases given penicillin, arsenic and bismuth, or penicillin and bismuth, reported by Jefferiss *et al* (1951), there were only 15 known relapses

Eames and Miller (1949) treated 1,022 patients in the British Army with 4 million units of penicillin plus one ten-week course of neoarsphenamine and bismuth There was a failure rate of 15 per cent at 18 months and there were many defaulters

In France, Marin *et al* (1949) combined 2 4 mega units of penicillin with Mapharside four times weekly for five weeks, and bismuth twice weekly for the same length of time They treated 230 patients who were followed up for 6 to 30 months In 36 seronegative primary infections the results were 100 per cent satisfactory, in 55 seropositive primary cases they were 90 per cent satisfactory, and in 94 cases of secondary syphilis they were 86 per cent satisfactory

O'Malley of Cape Town (1950) reported 365 cases of early syphilis treated with 2 4–4 0 million units of penicillin combined with arsenoxide on alternate days and bismuth twice weekly, all given over a period of eight days There were 12 failures

[illegible] the Rh [illegible]

years

Plotke *et al* (1950) treated 198 patients with secondary syphilis with 2 4 mega units of penicillin, eight daily injections of Chlorarsen and three of bismuth subsalicylate, given over eight days At 24–27 months, with 143 patients observed for a year or more, the failure rate was adjudged to be 20 per cent

Alexander *et al* (1950) employed a more intensive regime and gave to 219 patients 900,000 units of penicillin, 0 06 g Mapharsen and 3 ml of bismuth ethyl camphorate—all at one visit At one year 12 3 per cent of failures had been noted

Sixty nine patients were given 5 mega units of penicillin, 450 mg of [illegible] and Berdal (1950) [illegible] it In 470 patients [illegible] was a failure rate [illegible] chedule involving 300,000 units of oil beeswax penicillin daily for 16 days

Comparison of results of treatment with penicillin alone, and with penicillin, arsenic and bismuth

At the beginning of the penicillin era a number of workers considered that a combined treatment gave better results and that arsenic and bismuth

were worth retaining Thus Leavitt (1947), on reviewing the rapid treatment of 521 patients, concluded that penicillin alone was less effective

arsenic and bismuth with penicillin *during the same treatment period* Lentz (1949) likewise contrasted the results of a five-day schedule of penicillin alone with those of another employing arsenic in addition No significant differences in the results were noted

It is, however, likely that the older long term treatments with arsenic and bismuth were actually better than those of penicillin alone *for those that completed full treatment*, but only in so far as they reduced the risk of reinfection However, with the older treatments, few patients actually [illegible] was almost all [illegible] *et al* (1948) [illegible] there were no deaths and 240 treatment reactions, whereas in 118,544 patients treated with penicillin combined with arsenoxide there were 16 deaths and 1,632 severe reactions

The principal difficulty in comparing the results of different treatment-schedules of early syphilis is that the results of the treatment of sero-negative and seropositive primary syphilis, and secondary syphilis, are different For example, Walker and Utterback (1949) treated 109 patients on three schedules with only 60,000–300 000 units of penicillin At 34 months there were only 6 per cent of failures in the seronegative group [illegible]

[illegible] The cumulative retreatment rate at 24 months with procaine penicillin was 14 5 per cent, being similar at 13 6 per cent with penicillin and bismuth, and only [illegible]
However, it was f[illegible]
83 2 per cent giver[illegible]
69 8 per cent ha[illegible] did so Thus the better results apparently obtained by penicillin, arsenic and bismuth were offset by the higher default rate

During 1951 the British V D clinics formed a Co operative Clinical Group with the object of compiling collective data on a large scale

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(b) Penicillin and bismuth

Pardo Castello and Pardo (1950) reported 47 cases, and then 91 cases (1950*a*), of early syphilis treated with twenty daily doses of 500,000 units of crystalline penicillin G plus ten to twenty doses of bismuth subsalicylate given twice a week Of 45 patients observed for from ten months to two years the failure rate was only 1 2 per cent Only 39 patients in this series, however, had secondary syphilis The series was increased to 165 cases by Pardo and Pardo Castello in 1952

Alechinsky (1949) described a regime in use in Belgium in which 600,000 units of retard penicillin and 80 mg of bismuth camphocarbonate were given daily for 30 days After a rest of two weeks a further course was given to a total of two to four courses Jefferiss *et al* (1951) reported the results of 183 cases of early syphilis treated with penicillin and bismuth and found no great differences in a series of 561 cases treated by a similar schedule with neoarsphenamine in addition.

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(c) Penicillin, mercury and bismuth

Des Roseaux (1949) described yet another combined regime in which penicillin, bismuth and cyanide of mercury were each given daily for eight days

This blunderbuss regime exemplified an early French distrust for penicillin which has at last been dispelled For a long time they tended to regard the antibiotic as a useful adjunct instead of the mainstay of treatment As late as 1949 Veyre and Baylet summarized the French concept as follows (1) Treatment of attack—one year, (2) Treatment of consolidation—2–3 years, (3) After-control and treatment of insurance—3–4 years, and (4) Observation for life

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(d) Penicillin plus fever

[illegible]

2 4 mega units of penicillin plus three fever sessions of three hours each on alternate days They claimed better results with this means than those obtained with penicillin alone

Rodriquez *et al* (1949) had 13 1 per cent of failures at 12–15 months in 137 patients with early syphilis given penicillin and fever over a period of 30 hours

Penicillin has, however, proved an effective drug when given alone, and above all safer and more simple to administer Fever treatment requires admission to hospital and is not entirely without danger Hence its combination with penicillin for the treatment of early syphilis has not gained favour

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(4) Other antibiotics

(a) Aureomycin

Aureomycin is prepared from the mould *Streptomyces aureofaciens* It is produced in golden capsules each of 250 mg and it is administered

orally although it can be given parenterally Bacterial studies of this antibiotic were presented by Paine *et al* (1948) and by Meads *et al* (1948)

Wiggall *et al* (1949) did not consider that aureomycin was as powerful in rabbit syphilis as penicillin, but the results so far reported in the human disease have not been discouraging O'Leary *et al* (1948) described the healing of lesions in two patients given 44 2 and 67 5 g of aureomycin orally respectively Using smaller doses Willcox (1949), in Southern Rhodesia, reported the healing of lesions in nine Bantu, as did Irgang and Alexander (1948) with nine, presumably American Negro patients, given 1 g. intramuscularly daily for 20–23 days

O'Leary (1949) reported that serum levels of 2–4 microgrammes of aureomycin per ml, and that cerebrospinal fluid levels of 0 06–1 25 microgrammes per ml, were noted when 4 g of aureomycin was given daily for 12–18 days Aureomycin was also recovered from the blood of a newborn baby whose mother had been given this drug before delivery

Rodriquez *et al* (1949) treated 27 patients with dark field positive syphilis with 70 g of aureomycin over a period just exceeding 11 days, 18 patients were followed up for eight weeks and the serum tests showed a trend towards seronegativity By 1951 these authors had increased the series to 67 Olansky *et al* (1950) presented a larger series of 108 cases Of three cases of early syphilis given 240 mg/kg on one day all relapsed, but of 82 cases given 30 mg/kg daily for 4–9 days there were five relapses and five reinfections at 6–7 months An acceptable course was considered to be 60 mg/kg daily for eight days

Taggart *et al* (1952), after experience of 158 cases of syphilis treated with aureomycin, of which 98 were followed up for 12–15 months, considered that this course gave results comparable to those obtained by penicillin given intramuscularly over the same time A further 20 cases were reported by Robinson and Robinson (1951)

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(b) Chloramphenicol

This substance, now synthesized, is the same as Chloromycetin which is obtained from the mould *Streptomyces venezuelæ* It is produced in white capsules each of 250 mg

Robinson *et al* (1949) found that, when 1 g of chloramphenicol [illegible] 40 g, the lesions of 13 cases of [illegible] negative to the dark field in an [illegible] observed for more than a month became seronegative

Romansky *et al* (1949) treated 32 patients with early syphilis with 8–56 g chloramphenicol divided into doses given every 4 hours over 4–6 days They became dark field negative in 22–28 hours and the healing of lesions was prompt Only two patients were observed for as long as two months but already three had become seronegative and others were improving by that time Romansky *et al* (1951) increased their series to 90 cases and had satisfactory results when 60 mg/kg was given for 6–8 days Taggart *et al* (1952), on an experience of 104 cases of syphilis treated with chloramphenicol, also considered that for early syphilis an oral dose of 60 mg/kg given daily for 8 days gave results comparable to those of intramuscular penicillin

Robinson and Robinson (1949) treated five cases of dark field positive syphilis with doses varying from 3–48 g Treponemata disappeared from the lesions in 24–48 hours after 3 5–5 0 g had been given The same authors (1951) reported on 14 cases Two women were pregnant and produced healthy babies

Willcox (1949, 1950) employed much lower doses in an experimental series on four African patients and also noted the rapid disappearance of spirochætes from the lesions Only 1 75–3 0 g was given over 3–5 days

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(c) Terramycin

Robinson and Robinson (1951) treated five cases of early syphilis with 24 5–48 0 g terramycin over 15 days, and followed them up for 2½–13 months Of the four cases followed up for nine months or more, one underwent a serorelapse at nine months and the remainder were well

given 1 g terramycin four times daily, the spirochætes disappearing within 24 hours One other case was reported by Willcox (1951)

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(d) Side effects of the oral antibiotics

With orally administered drugs, unlike penicillin, the physician can never be absolutely sure that the prescribed dose is safely absorbed within his patient The oral antibiotics, also, are not free from side effects and these may be grouped as follows

Gastro intestinal

Nausea and sometimes vomiting may occur with all, perhaps most often with aureomycin Likewise diarrhœa, which may persist for some days, is not uncommon

Avitaminosis

The production of the vitamin B complex may be hampered as a result of

or when the drugs are taken for long periods of time

Shift in the bacterial spectrum

With the suppression of certain bacteria other organisms may flourish once their inhibiting influences have been removed The appearance of

pulmonary moniliasis in patients (usually with lung abscess or bronchiectasis) being treated with these drugs led in the U S A to the ruling [illegible]

resulting from a thrush colony sealing off a partially obstructed kidney following treatment with chloramphenicol These cases are fortunately rare A fairly common minor complication, however, is pruritus ani with a burning feeling in the rectum and which Willcox (1951) first reported with terramycin under the title of 'ano-rectal syndrome' The same condition occurring after aureomycin, chloramphenicol and terramycin was reported in the U S A by Manheim (1951)

Sensitization reactions

Most drugs produce skin complications in susceptible subjects The writer has had a patient who developed a large macular rash with aureomycin, which subsided on discontinuing the drug, only to reappear when terramycin was given A case of anaphylactic shock, with generalized œdema and itching, occurring half an hour after taking chloramphenicol, was reported by Patterson (1950)

Blood dyscrasias

These reactions are confined to chloramphenicol which has a nitrobenzene radical in its structure Rich *et al* (1950), Wolman (1952) and Hawkins and Lederer (1952) have all reported cases of aplastic anæmia following its use, a serious complication which may prove fatal Subcutaneous hæmorrhages may be observed Since this time a number of similar cases have been recorded

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CHAPTER IX

LATE LATENT SYPHILIS, LATE BENIGN SYPHILIS AND CARDIOVASCULAR SYPHILIS

A. LATE SYPHILIS: GENERAL

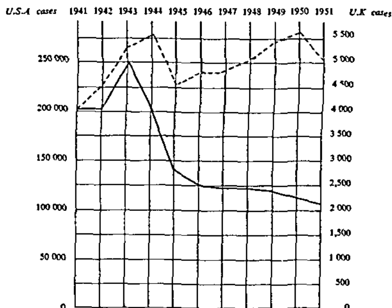


FIG 10—TRENDS IN THE INCIDENCE OF LATE AND LATE LATENT SYPHILIS IN CONTINENTAL U.S A AND ENGLAND AND WALES

(From Ministry of Health, London, and United States Public Health Service figures)

——— Continental U S.A scale on left. - - - - - England and Wales scale on right

U S A fall from 1943 peak = 57·6% in 8 years

U K fall from 1944 peak = 9·9% in 7 years

FIGURES FROM WHICH GRAPH IS COMPILED

	U S A.	U K		U S A	U K		U S A	U K
1941	201,190	4,050	1945	142 731	4,546	1949	121,933	5,470
1942	202,216	4,561	1946	125,836	4,821	1950	113,174	5,601
1943	252,995	5,381	1947	122,257	4,618	1951	107,133	5,033
1944	203,396	5,588	1948	123,972	5,085			

Greece, Messinezy (1949) reported
ctant mothers in Athens Rosenthal
ive reactions in New York Likewise,
cent of positive reactions in 6,809

amongst the Norwegian occupying
were discovered by means of routine
from this that every fifth male acquir-

tuarial approach of contrasting the
with those of the whole population

d 2,566 cases of latent syphilis, of
s or more They concluded that a little
outcome when latent syphilis was
was considered by Jordon and Dolce
r 10 years or more Complications
rly treated group, but only two cases
sm were noted in 100 well treated
mortem material from 380 syphilitic
en treated Anatomical lesions of
those untreated, but only 23 2 per
There was thus close agreement with
records of his predecessor, Boeck

pulmonary, cardiovascular and
better condition in the controls
abama series by Pesare *et al*
d and left untreated in 1931
ter some years Nielson (1950)
yphilis for 29–36 years
syphilis are in reality cases of
the new tre ma immobiliza
value in their tion. Heywood
the serum late and
chronic b tive

in top gear by 1943. The development of case finding measures in Great Britain has been more slow.

The mortality from late syphilis has progressively declined and this decline was well in evidence both in Britain and the U.S.A. before the introduction of penicillin. It has markedly affected G.P.I. and tabes dorsalis although the deaths from aneurysm have not diminished (Figs. 11 and 12). The fall in respect of general paralysis and tabes dorsalis may be

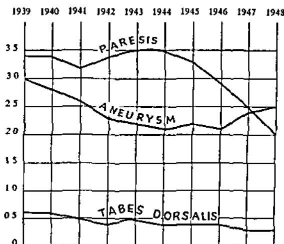


FIG. 12—*DEATHS FROM SYPHILIS IN CONTINENTAL U.S.A.*
(Rates per 100 000 population)

FIGURES FROM WHICH GRAPH IS COMPILED
(United States Public Health Service figures)

	Paresis	*Tabes*	*Aneurysm*
1939	3.4	0.6	3.0
1940	3.4	0.6	2.8
1941	3.2	0.5	2.6
1942	3.4	0.4	2.3
1943	3.5	0.5	2.2
1944	3.5	0.4	2.1
1945	3.3	0.4	2.2
1946	2.9	0.4	2.1
1947	2.5	0.3	2.4
1948	2.0	0.3	2.5

related to the greater use of diagnostic lumbar punctures and the treatment of potential cases in the presymptomatic stages, better methods of treatment, and the introduction of sulphonamides and other drugs for the treatment of pulmonary and urinary complications.

B. LATE LATENT SYPHILIS

The incidence of latent syphilis, but including early latent syphilis, may be determined by routine serum tests. The incidence of positives differs widely throughout the world, but is low in the highly developed countries.

For example, of premarital serum tests performed on 11,997 persons in Saskatchewan only 32 were positive and 14 persons had already received treatment (Doyle, 1949). In Bergen, during the years 1944–1948, only 44 positive tests (0.61 per cent) were found by Idsøe and Vogelsang

(1950) in 10,647 pregnant women In Greece, Messinezy (1949) reported 1 1–2 5 per cent of positives in expectant mothers in Athens Rosenthal *et al* (1950) found 6 6 per cent of positive reactions in New York Likewise, Price (1952) reported only 0 67 per cent of positive reactions in 6,809 pregnant women tested in London

Of 202 cases of recent syphilis amongst the Norwegian occupying forces in Germany no less than 40 were discovered by means of routine [illegible]

was open to challenge

Blum and Barnett (1948) reviewed 2,566 cases of latent syphilis, of which 316 were followed up for 9 years or more They concluded that a little treatment was better than none The outcome when latent syphilis was poorly treated, or not treated at all, was considered by Jordon and Dolce (1946) who followed 169 patients for 10 years or more Complications developed in 39 2 per cent of the poorly treated group, but only two cases of aortitis and two cases of aneurysm were noted in 100 well treated persons Rosahn (1946) examined post-mortem material from 380 syphilitic patients, 198 of whom had never been treated Anatomical lesions of syphilis were found in 38 9 per cent of those untreated, but only 23 2 per cent [illegible]

[illegible]

systems of the two groups, the ocular, pulmonary, cardiovascular and genito-urinary systems were generally in better condition in the controls Similar findings were reported in the Alabama series by Pesare *et al* (1950) 410 syphilitic persons were located and left untreated in 1931 and a number of these [illegible] n (1950)

[illegible] cases of false positive reactions is undoubted, but the new treponema immobilization test (p 80) is [illegible]
(1952)
latent [illegible]

serum tests for syphilis were usually in fact treated Thomas *et al* (1950), having treated 127 cases of supposedly latent syphilis with penicillin, reviewed their reactions to ordinary serum tests after 1–4 years They concluded that four out of five patients actually had had syphilis, but that the remainder had probably been examples of biological false positive serum reactions

Serum reversal after treatment with penicillin is not to be anticipated as the probable outcome in late latent syphilis, any more than was the case with the older methods of treatment with arsenic and bismuth In a study of 120 late and latent syphilitics by Willcox (1947) it was noted that in cases where serological titre had improved on previous treatment with arsenic and bismuth and later relapsed, it improved again after penicillin, but where it had already proved resistant it remained so The serological pattern in late and latent syphilis was also reviewed by Redmond *et al* (1952), and penicillin was considered by Lindemayr (1950) no more successful in producing sero reversal than the arsenicals

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C. LATE BENIGN SYPHILIS

In the year 1931 in Alabama 410 syphilitic persons were clinically and serologically examined, as were 201 controls, and all were subsequently left untreated During 1938–1939 some 140 of the untreated syphilitics and 156 of the controls were again examined *Those syphilitics who had* meanwhile sought treatment were excluded During 1948 Pesare *et al*

(1950) located and made a third examination of 155 of these persons At the time of the first examination 47 2 per cent of the untreated syphilitics and 26 1 per cent of the controls showed some abnormalities At the time of the second examination after deaths had been added the figures were 52 per cent for those with syphilis and 37 3 per cent for the controls At the time of the third examination they were 89 1 and 61 1 per cent respectively A note on the patterns of quantitative serological tests in late syphilis was made by Willcox (1947) and by Redmond *et al* (1952)

Gummata

Gummata occurring no less than 43–60 years after infection were noted by Wiggall and Hahn (1949) A case of gumma of the spinal cord which simulated tumour was recorded by Thompson and Preston (1950) and a gumma of the eyelid resembling chalazion was reported by Cassady (1950) A case of Mikulicz s syndrome caused by syphilis was recorded by Heckler (1950) A case of gumma of the sternomastoid was reported by Kierland and Underwood (1948) Thomas and Rook (1949) reported a case of house maid s knee resulting from gummatous syphilis Polayes (1950) reported a case of gumma of the breast mistakenly diagnosed as cancer

Thirty four cases of various gummata were treated with penicillin by Tucker (1948) w [illegible]
were treated by
daily doses of 1
complete healing in one and partial healing in three

Employing oral aureomycin O Leary *et al* (1949) and Kierland *et al* [illegible]

by Willcox (1952) (For the superinfection theory of the causation of gummata see Chapter XII p 162)

Bone

A survey of the radiological aspects of bone syphilis was made by Gaskell (1951) A case of syphilitic osteo periostitis involving the flat bones—the skull ribs and phalanges—was described by Metcalfe (1949) A case of destructive osteomyelitis occurring early in the disease was reported by Cox (1950) McGladdery (1950) reported five cases of bone syphilis in young adults in which osteoporosis was more marked than new bone formation The literature concerning bone syphilis was reviewed and three other cases were described by May and Breck (1950) Three cases of recurrence of skin and osseous gummata after treatment with penicillin were reported by Reynolds (1948) Crowe and Johnson (1951) reported the successful treatment of a fifty nine year-old female with osteo-periostitis with 50 g of aureomycin

Skin

The healing of a cutaneous syphilide by oral penicillin was noted by Wallace and Paul (1946) A case of precocious tertiarism, appearing as a nodulo cutaneous syphilide only 18 months after the patient had received 600 000 units of penicillin for what was in retrospect considered to be

et al (1950) A case of [illegible] papules with central depressions on th[illegible] presented by Saunders and Youngstrc[illegible] gummata to aureomycin was described by Kierland *et al* (1950) and by Olansky *et al* (1950), and to terramycin by Willcox (1952)

Lung

Four cases of pulmonary syphilis were presented by Kulchar and Windholz (1947), and a fatal case in which *T pallidum* was demonstrated by Wilson (1946) A further case in a Moroccan was described by Decrop and Cabanie (1949), and others were reported by Sanchez Barriga Carapeto (1949), Librach (1950), Smith *et al* (1950), Susman (1951) and Hollingsworth (1951)

Stomach

A comprehensive review of the literature concerning gastric syphilis was presented by Palmer (1949) Of a series of 3 066 cases of peptic ulcer reported by Kirsner *et al* (1950), 52 (1 7 per cent) were considered to be syphilitic Decreased acidity or anacidity was noted in 42 A case of precocious tertiarism, with a specific granulomatous infiltration of the stomach in early syphilis, was reported by Bell (1951)

Liver and spleen

Shapiro and [illegible] of the liver [illegible] the liver was [illegible] jaundice in syphilis were classified by Brass and Moser (1949)

syphilitics were presented by Hambrick and Smith (1949) Abdominal syphilis in general was considered by Nicol (1952)

Kidneys

Although syphilitic nephrosis is more commonly an accompaniment of secondary than of late syphilis, it is for convenience considered here

Two successfully treated cases were reported by Thomas and Schur (1946), and another by Olansky and McCormick (1947) who also reported an additional case cured by intensive arsenotherapy One case described by Scott and Clark (1946) developed the complaint five days after treatment with penicillin had been concluded, and the condition was considered to be a focal Herxheimer reaction

[illegible]

in one, and partial success in another

Eyes

In syphilitic *iritis* cortisone has been used to good effect Horne (1951) had good results in three cases treated by a suspension containing 5 mg/ml An inexpensive and effective method of using cortisone is by subconjunctival injection which was used on nine patients by Koff *et al* (1950) One case of iritis treated by Wilson (1951) also responded

Others

Syphilis of the *oral cavity* was considered by Horne (1952) and by Lloyd (1951) Of 100 cases of gummatous ulceration of the palate, fauces or [illegible] he tongue was [illegible] by Hudson and [illegible] *al syphilis* was reported by Suchett-Kaye (1950)

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[illegible]
[illegible] –3
[illegible] –46

D CARDIOVASCULAR SYPHILIS

(1) Clinical

A case of syphilitic arteritis causing gangrene of the toes was recorded by Moynahan (1948)

General reviews concerning aortic syphilis were presented by Moore

considered that cardiovascular syphilis comprised 13–15 per cent of all cardiac cases seen at autopsy Of 41 patients with aneurysms 70 per cent survived until their fiftieth birthday Of 59 other cases of aortic aneurysm, Chapman and Morgan (1947) reported that only 15 gave a history of primary chancre, and that no treatment had previously been given to 40, the remainder had received inadequate treatment Jordon and Dolce (1947) investigated 64 cases of syphilitic aortitis and 113 others com-

co existed

Webster and Reader (1948) examined microscopically the aortas of 45 subjects with post mortem evidence of active or healed syphilitic aortitis 19 of these had received adequate anti-syphilitic treatment with 20 or more injections each of arsenic and bismuth, 7 had had less, and 19 had had no treatment at all Only 3 of those adequately treated showed active inflammation which was, however, present in 3 of 5 of those inadequately treated, and in all of 19 of those untreated

Reader *et al* (1947) followed up 47 patients for 2–16 years with aortic insufficiency, who had been intensively treated with trivalent arsenic and bismuth After a 5½-year period 20 patients were worse, of whom 13 had died of heart disease, but 27 were still living, 12 being asymptomatic Gelfand and Bellet (1951) studied in detail the musical murmur of aortic insufficiency in 18 cases

A case of syphilitic saccular aneurysm in a thirty-one-year-old white man, who had shown

Two cases of rupture of an aortic aneurysm into the superior vena cava were reported by Morris (1950), and another with rupture into the pulmonary artery by Klein and Porter (1950) Estes (1950) collected 102 cases of aneurysm of the abdominal aorta, of which 97 were due to arteriosclerosis, 1 to syphilis, 3 to both diseases and 1 to trauma Finestone (1949) described one case of syphilitic aneurysm of the abdominal aorta which ruptured into the stomach Gordon Taylor (1950) discussed the surgery of aneurysm of the innominate artery and presented two cases due to syphilis

art

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artery associated with cirrhosis of the liver by Engel (1951); a case of
artery by Grelland (1950), and one
mpression of the pulmonary artery
fifty-three-year-old Negro was des-

Three cases of gumma of the heart were reported by Kothare (1949), and a case of complete auriculo-ventricular block in a coloured woman aged twenty-five by Pick and Fishman (1950) A case of a localized syphilitic aneurysm of the descending branch of the left coronary artery, in an eighty-one-year-old Negro who died of myocardial infarction following complete thrombosis of the aneurysm, was recorded by Denham (1951). *Two cases of syphilitic aortitis with mural thrombi leading to bilateral* coronary occlusion were described by Volk *et al* (1950) Seven cases of myocardial infarction due to syphilitic ostial stenosis of the coronary arteries, two with coronary atheroma in addition, were reported by Scharfman *et al* (1950)

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(2) Diagnosis

... presence of linear areas ... Thorner et al (1949) ... of 122 cases of aortic syphilis proved later at autopsy, whereas it was present in only 2 per cent of persons with uncomplicated atherosclerosis Elkeles (1949) also presented a case of syphilitic aortitis showing aortic calcification

From a study of 20 patients showing aortic calcification in routine chest films, and from the consideration of 200 control films, Jackman (1950) ...

... of eleven patients with aortic insufficiency Angiocardiography, as applied ...

... may all produce elongation of the aorta, but Dotter et al (1950) pointed out that in syphilitic aortitis the elongation is disproportionate in the ascending aorta Peabody et al (1950) studied 83 patients with late syphilis of whom 49 were shown to have cardiovascular syphilis, but only in 34 was the condition discovered without the aid of the angiocardiogram

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(3) Treatment

The ...

(1951)

Reader *et al* (1947) followed up 47 patients with aortic insufficiency who had been intensively treated with trivalent arsenic and bismuth for 2–16 years During a 5½-year period 20 changed for the worse of whom 13 died of heart disease, but 27 were still living of whom 12 were asymptomatic

Barnett and Small (1950) appraised the results of the older methods with arsenicals and bismuth in 384 cases and considered that treatment improved prognosis at all stages The results of treating 73 cases with mercuric cyanide for long periods of time were described by Gerbaux (1949) Several courses of 50–100 intravenous injections given once daily were recommended but this drug is seldom used today

It is still too early to appraise accurately the value of penicillin in the treatment of aortic syphilis although *every case of syphilis deserves a course of penicillin* The risk of therapeutic shock (Jarisch Herxheimer reaction) at the onset of treatment with penicillin has prompted many physicians to commence with a preliminary course of 4–6 weeks duration of

vas e

cor e

that such preliminary treatment will actually prevent a later Herxheimer reaction with penicillin is not entirely convincing

Tucker and Farmer (1947) considered that the risk of therapeutic shock was exaggerated but even so of 26 patients with cardiovascular syphilis treated with penicillin five had febrile bouts and two had a worsening of anginal pain Edeiken *et al* (1949) noted seven examples of a febrile Herxheimer reaction one with a sense of constriction in the chest in addition in 50 patients with aortic regurgitation and/or aneurysm treated with 1 2 9 6 million units of penicillin Thirty nine of these however had co existent neurosyphilis—which condition may also be associated with febrile Herxheimer reactions Fatalities following the use of penicillin have been reported by Scott *et al* (1949) by Diefenbach (1949) who presented a case showing a sudden expansion of the aneurysm with occlusion of the left bronchus on the third day of treatment with penicillin by Whorton and Denham (1951) who reported the death of a twenty seven year old Negro woman with gummatous aortitis and aortic insufficiency 27 hours after commencement of antisyphilitic treatment with penicillin and by Butterly and Fishman (1952) who reported a case of coronary occlusion in a white woman

On the other hand Flaum (1949) and Flaum and Thomas (1949) reporting 50 cases of cardiovascular syphilis treated with or without preliminary bismuth considered that the danger of therapeutic shock had been over emphasized Because of the Herxheimer reaction it has been a

12 such cases simultaneously with digitalis and penicillin commencing

three

shock

failure

iscular

syphilis treated with penicillin (4 8–9 6 mega units) Of 34 cases of [illegible]

[illegible] are unchanged

them Seven of nine patients with aortic regurgitation and aneurysm remained under observation for 8–38 months with four improved and one unchanged There were two deaths Four of five patients who had angina before treatment were improved Treatment was practically never interrupted

Sinclair and Webster (1951) treated 53 patients with penicillin, and the only evidence of a Herxheimer reaction noted was a rise of temperature They believed that penicillin alone should be used Breutsch (1951) considered that penicillin alone without premedication was the logical treatment but that perhaps 600 000 units a day for 7 weeks might be necessary He expressed doubts whether arsenic and bismuth were ever beneficial in this complaint

Wheeler and Curtis (1951) had no adverse reactions to penicillin in 21 cases and did not believe that there was any convincing evidence of them in the literature Johnson and Shapiro (1951) also considered metallotherapy unnecessary but recommended in the case of heart failure that penicillin should not be given until after cardiac compensation had been established Their 17 patients treated received only 1,000 units 3 hourly on the first day, and this dose was gradually increased to 40,000 units by the eighth day One patient with a large aneurysm died two days after the completion of treatment

Penicillin given for latent syphilis does not necessarily prevent the occurrence of cardiovascular syphilis Reynolds (1948) noted a patient with aortic regurgitation which appeared 16 months after receiving 8 million units of penicillin Mohr and Hahn (1952) reported four cases of aortic insufficiency developing 6–18 months after penicillin therapy, indicating either progression in spite of treatment, or therapeutic paradox

Surgical methods in the treatment of aortic aneurysm are not yet entirely satisfactory, but with modern advances in cardiac surgery improvements are expected

Borrie and Griffin (1950) described 24 cases of aortic aneurysm and three with innominate aneurysm Colt's method of wiring was used on nine patients, and two with fusiform aneurysm of the descending aorta were treated by cellophane wrapping *A case treated by the cellophane method* was recorded by Shallard (1949), and another of a fusiform aneurysm of the abdominal aorta treated with polythene cellophane by Middleman and Drey (1951) The ability of polythene dicetyl phosphate to cause proliferation of fibrous tissue was made use of by Cowley *et al* (1951) in another case of aortic aneurysm with sternal perforation

Two cases of aneurysm of the abdominal aorta treated by a procedure known as 'cutis grafting', whereby an attempt was made to encircle the aneurysm with cutis, were described by Lowenberg (1950) Babcock (1950) described an operation whereby the carotid artery was anastomosed to the jugular vein in order to reduce the pressure within the sac

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CHAPTER X

NEUROSYPHILIS

A. CLINICAL

(1) Paresis

WILSON *et al* (1950) analysed the results of 339 autopsies of neuropathic patients with serological or post mortem evidence of syphilis, and decided that syphilis could be incriminated as a possible cause of mental deterioration in 176 In the American Negro, Ivins (1950) reported that the psychoses most commonly encountered were those due to neurosyphilis and to alcohol Willcox (1951) investigated the relation of neurosyphilis and psychoses in the African Negro

Hughes (1948) assessed the results of treatment in 712 neurosyphilitics admitted to an American State Hospital over a period of 14 years, 87 5 per cent of whom had paresis Of these, 43 4 per cent died and 21 6 per cent were released on parole Grover (1948) emphasized that the failure of a paretic psychosis to improve with treatment should not necessarily be regarded as a treatment failure, for an active syphilitic process may indeed be arrested but only after permanent damage has been done to the brain Kirman (1947) reported on the status of 42 paretics after 6–18 years in hospital, in all but seven the cerebrospinal fluid was normal

Sternberg and Zimmerman (1950) presented an analysis of the results of the Wechsler Bellevue adult scale of intelligence as applied to 66

hometric

mental

[illegible]yman *et al* (1951), and Patterson *et al* (1950), studied the cerebral blood flow, oxygen consumption and cerebral resistance of neurosyphilitics They found that the cerebral blood flow was reduced to 72 per cent of normal [illegible]

r[illegible]

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f [illegible] in part explain the benefit brought about by such treatment

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W (1950),

(2) Tabes dorsalis

A form of tabes dorsalis due to acute degeneration of the posterior root ganglia, presenting with a generalized sensory loss, was described by

who presented an extensive review of the literature and details of 11 cases Laryngeal involvement had an incidence of 1–3 per cent in 1,500 tabetics The common form is an asymptomatic unilateral posticus palsy

T A B vaccine, indicating how this procedure could aid diagnosis Fowler (1947) claimed that the injection of procaine or Proctocaine as near as possible to the apparent site of lightning pains resulted in a number in an apparent lengthening of the duration between bouts and a reduction in their severity Horton (1951) reported a case in which lightning pains were relieved by histamine injections Lobotomy was performed with some measure of success to relieve intractable pains in a case described by Smolik (1951)

Grimble and Csonka (1952) described a case of silent gastric perforation in a tabetic Stoops *et al* (1948) stated that supradiaphragmatic vagotomy

Lichtman (1951)

Diez Rivas (1949) found that the Kepler water test was positive in nine patients with tabes dorsalis i e the total volume of the night urine specimen was greater than any four specimens voided on the following day

controls

References

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d School,

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(3) Optic atrophy

... were presented by Graveson (1950)

Optic atrophy and other forms of ocular syphilis were discussed by Klauder (1951) Fifty-four cases of syphilitic optic atrophy were reviewed by Levin *et al* (1947) Kant (1949), in a study of this condition, counted the capillary vessels on the disc

... of the perimeter

time of the first examination (Klauder *et al* (1948), Klauder and Gross (1949))

malaria went blind within two years, whereas of 75 left untreated only

of which 15 were followed up for two years or more Penicillin alone seemed as effective in preventing progression as when combined with fever, although the regression of existing atrophy is not to be expected with any treatment

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(4) Other forms of neurosyphilis

Eighty cases of early syphilitic meningitis were reported by Pardo and Farmer (1948) who found no incidence of later parenchymatous neurosyphilis in 15 patients followed up for 5–20 years after treatment with arsenic and bismuth

The clinical syndrome of occlusion of the posterior inferior cerebellar artery, which may occasionally be due to syphilis, was described by Levine *et al* (1949) Two case histories of syphilitic wrist drop were recorded by Heathfield and Aldren Turner (1951)

Considerable interest has attended the question of neurosyphilis in the African Many have alleged that the incidence is low and have attempted to explain this on grounds of racial susceptibility, treponemal variations, or abortion of neurological involvement by endemic malaria Recently others have denied that the incidence is as low as was first thought

Lambkin (1908, 1908*a*) made a venereal disease survey in Uganda and

of syphilis in 338 (11 3 per cent) of 2,994 post mortems performed in Uganda Syphilis had been the cause of death in 261 cases and signs of neurosyphilis were found in 154 of these He also stated that 0 4 per cent of patie
Trowell
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while no typical case of tabes or paresis was encountered, a number of [illegible] were observed, who were being treated [illegible]

[illegible] syphilis in West Africa, and the confusion with trypanosomiasis, were stressed by Willcox (1946) Gelfand (1948), writing from Southern Rhodesia where trypanosomiasis is no pressing problem, stated that meningovascular syphilis is the most common form of neurosyphilis in Africans and that tabes and paresis are relatively infrequent

On the other hand Loewenthal (1939) reviewed the question of neurosyphilis in Africa and stated that the condition was rarely found at postmortem, as did Becker (1946) Cook (1948) encountered the same belief as to the rarity of neurosyphilis in the Negro in Trinidad He examined the spinal fluids of 1,028 patients with repeatedly positive serum tests for syphilis Positive spinal fluids were noted in 153 patients (14 9 per cent), but only in 27 cases were the changes marked Of 527 patients clinically examined 82 were considered to have neurosyphilis It was concluded that neurosyphilis in the tropics is not rare and that a more general use of spinal fluid examinations would reveal much of that which is hidden

Willcox (1951) reported the examination of 117 spinal fluids of asylum inmates during a venereal diseases survey of the African in Southern Rhodesia and found 32–36 cases of possible neurosyphilis The same writer (1951*a*), from an examination of the spinal fluid of 55 epileptic Africans, could find no evidence that syphilis was responsible for the bulk of African epilepsy Neither did the serum findings in a large mental hospital show any higher incidence of positives in epileptics He affirmed that neurosyphilis in the African usually assumed the meningovascular form, and that paresis and tabes dorsalis were relatively uncommon It was felt that the more extended use of the lumbar puncture would confirm the fact that neurosyphilis in the African is not uncommon

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(5) Lumbar puncture

The evaluation of the results of the spinal fluid examination was discussed by Dattner (1948) Simultaneous lumbar and cisternal punctures were performed on 102 patients by Davis *et al* (1951) There were few differences as to cell count except in the presence of pleocytosis, a higher count being then noted in the lumbar fluid Higher protein values and greater reactivity to the mastic test were found in the lumbar fluid

Cecil and Johnwick (1951), in a review of 44,711 diagnostic cisternal punctures performed over five years, reported four deaths attributable to the procedure and did not consider that there was any justification for its retention

Serious sequelæ of lumbar puncture are few, although Olansky (1949) reported a rare complication—that of extradural hæmatoma This resulted in paraplegia, and a laminectomy was performed Minor after-effects are, however, common—especially headache

Sciarra and Carter (1952) performed lumbar punctures with an 18 gauge needle In 45 instances no fluid was removed and the incidence of headaches was 38 per cent Of 62 other patients, from whom 10–12 c c of fluid was removed, 46 per cent developed headaches It was concluded that the amount of fluid removed made little difference to the incidence of headaches Marshall (1950) also investigated this condition and performed a second lumbar puncture on 43 patients already suffering from a lumbar [illegible]

obscure as ever

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B. TREATMENT

(1) Penicillin

(a) Intramuscular penicillin

The series reported from Philadelphia by Stokes *et al* (1948) of 361 cases of neurosyphilis treated with intramuscular penicillin, and by Stokes *et al* (1949) after five

to 519 cases by

unsupported by

patients treated since 1943, 32 are known to have died but in none was

fluids from patients with paresis, and 60–70 per cent from patients with tabes dorsalis, had completely or nearly reached normality

Dattner (1948

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units of penicill

satisfactory and only three per cent were true failures The same author (1949) found that only 45 out of 388 patients treated with 2 9 million units and followed up for 6–56 months failed to achieve a satisfactory status Dattner (1950) described in detail three cases which failed to respond to penicillin in the usual doses

By 1951, Dattner *et al* reported on 438 patients with active neurosyphilis treated with penicillin The spinal fluid became inactive and remained so for 6–75 months Fifteen daily injections of 600,000 units were

Other

ated 444

excellent

led Rose

who had

been in hospital for an average of 22 months, during which time they received tryparsamide and bismuth, returned to the community 2½–6 years after receiving penicillin with or without fever

On the other hand the U S Army Medical Department (1946) recommended a course of nine million units of penicillin given over 22 days, followed by quarterly blood and cerebrospinal fluid examinations, as a standard pattern of treatment for neurosyphilis In cases of paresis,

taboparesis, eighth nerve deafness, syphilitic epilepsy and Erb's paraplegia, however, the addition of 8–12 fever sessions was also recommended

Moore and Mohr (1946), writing of asymptomatic neurosyphilis, noted that the earlier that the treatment was given the better were the results The cell count, protein content and Wassermann reaction of the spinal fluids fell to normal after treatment in 27 of 35 patients in whom the infection was of less than four years' duration, but in only 8 of 43 of those whose infections had been in existence for longer than four years Ford *et al* (1951) reported on the results of treating 112 patients with asymptomatic neurosyphilis with 4 8 mega units over eight days There were ten treatment failures Nine mega units of penicillin over ten days was recommended as a satisfactory course

In long standing cases the improvement is striking only in the cerebrospinal fluid Scully *et al* (1948) emphasized that the spinal fluid response

so called 'inactive' spinal fluid He claimed clinical improvement in ten and improvement in the spinal fluid of four

For syphilitic nerve deafness, Tamari and Itkin (1951) did not consider that penicillin was a superior drug to those previously used In spinal syphilis treated with penicillin Jones *et al* (1951) noted that patients with meningomyelitis of less than three months' duration did well, but those cases due to vascular occlusion fared badly

The success of penicillin given for early syphilis in preventing future neurosyphilis was emphasized by Altshuler *et al* (1949) who found only 21 abnormal spinal fluids in 30,972 patients previously treated for early

fifteen daily injections of 600,000 units are recommended

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(b) Intrathecal and other methods of penicillin administration

It was at one time stated that penicillin given intramuscularly did not penetrate into the cerebrospinal fluid, although this statement has since been contradicted Redfearn *et al* (1949) found penicillin in bactericidal concentrations in 70 per cent of 132 samples tested, while Boger and Wilson (1949) found demonstrable quantities in the spinal fluid of 14 of 18 patients two hours after the injection of 500,000 units

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of intramuscular and intrathecal penicillin, plus consolidatory bismuth and fever therapy The results obtained with this blunderbuss regime can scarcely be advanced as an argument in favour of the intrathecal administration of penicillin Many regard this as an unnecessary and dangerous mode of ...

only 40,000 units being given daily for 25–30 days It was claimed that penicillin had an enhanced effect when given by this means

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(c) Herxheimer reaction

A number of reports have concerned serious Herxheimer reactions stated to follow the use of penicillin Although some fatal cases have been recorded it must not be forgotten that their incidence is extremely low considering the vast number of neurosyphilitics treated with penicillin Attempts to avoid this reaction have been made either by commencing penicillin treatment with a very small dose, or by a preliminary course of 4–6 weeks of bismuth with or without iodides The Herxheimer reaction in some respects is an 'all or none' phenomenon and it is by no means certain that small doses of antisyphilitic drugs, themselves insufficient to produce a Herxheimer response, will *prevent such a reaction when more* potent doses are later given

The febrile F

penicillin was s

Farmer (1948)

syphilitics Lereboullet and Sapin Jalloustre (1947) reported a fatal example in a paretic showing Jacksonian epilepsy and hemiplegia Stokes *et al* (1948) considered that Herxheimer reactions may sometimes result in serious damage, and they tried the giving of only 500 units of penicillin at the commencement of treatment

Tucker and Robinson (1946) reported two examples of a Herxheimer reaction, one showing fever and convulsions, and the other meningeal irritation, occurring 30 hours after the commencement of treatment One patient had clinical paresis and the spinal fluid of the other had a paretic formula A fatal example in a patient diagnosed as having early syphilitic meningitis, but proved at post mortem to have a gummatous lesion, was recorded by Scott *et al* (1949) Shaffer and Shenkin (1950) reported a further fatal case in a patient with syphilitic pachymeningitis after 13 injections of only 1,000 units of penicillin had been given at intervals of three hours Two other severe cases were reported by Epstein and Key (1949)

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(2) Fever therapy

Breutsch (1949) considered that the beneficial action of malaria on paresis was not due to the malaria itself but to an additional factor which stimulated the reticulo endothelial system (this might be cortisone) The use of blood parasite counts for the better control of therapeutic malaria was urged by Kaplan and Read (1948) Welch *et al* (1948) found that mepactine was inferior to quinine in terminating the paroxysms of artificially produced malaria One danger of malarial therapy, if inoculations of blood from infected patients are employed, is the possibility of transferring the virus of homologous serum jaundice Four patients so affected were

[illegible]

malaria

On a small series of cases, Watson (1949) considered that fever induced by malaria gave better results than fever induced by T A B vaccine Noojin *et al* (1950) showed how, by giving 20 million organisms of T A B

[illegible]

cent, and an improvement in 84 per cent A remission in the spinal fluid findings was noted in 72 per cent, and improvement in 25 per cent

Epstein and Key (1949) reported on 87 cases of neurosyphilis treated with penicillin and fever induced by an electric blanket Epstein and Allen (1951) reported on a larger series treated by this method The use of an electric blanket to induce fever was also described by Willcox and Flynn (1951) Kawamura and Ueda (1944) gave pyretotherapy to ten cases of tabes dorsalis by means of intramuscular injections of a suspension of the testicle of a rabb [illegible]

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(3) Penicillin alone versus penicillin plus fever

In pre penicillin days chemotherapy plus malaria gave better results than either measure alone (Hughes, 1948) It was not surprising, therefore, that fever should have been combined with penicillin in the treatment of neurosyphilis From the introduction of penicillin there were few to say that it was inferior to fever, but there were many who considered that better results could be obtained by a combination of both By 1950, however, the voices of yesterday which had advocated penicillin *plus* fever were muted *if not silenced, and most clinicians today first give penicillin alone a trial* before resorting to the more dangerous method which necessitates admission to hospital

there was a greater tendency for a positive Kahn test (often stated to be an unsatisfactory test on spinal fluids) to persist in the spinal fluid for longer in the group treated by penicillin alone Earlier the same group (Curtis and Horne (1948) and Curtis *et al* (1948)), having observed 108 cases of neurosyphilis treated with penicillin alone, and 115 others treated with penicillin and fever, concluded that cases of asymptomatic neuro syphilis, meningovascular syphilis and tabes dorsalis did as well with penicillin alone as with penicillin and fever, but that patients with paresis

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The Philadelphia school have consistently remained loyal to penicillin alone, after reporting 361 cases treated (Stokes *et al* (1948)), 519 cases (Gammon *et al* (1950)), and 603 cases (Ingraham *et al* (1950)) Epstein and Allen (1951), on an experience of 81 cases, also found penicillin alone to be excellent but recommended that fever be added in cases of paresis, taboparesis, optic atrophy and in those cases which failed to respond to penicillin alone

On the other hand Spiller and Stewart (1950), on an experience of 170 patients treated, and Callaway *et al* (1950) on 207 patients, considered that there was little to be gained by increasing the dose of penicillin beyond four million units, or by the addition of fever

Nichols and Heyman (1949), on a basis of 298 cases, found that penicillin G gave rather better results than penicillin in oil beeswax and recommended that malaria should not be used until penicillin had had a fair [illegible] atrophy or other severe symptoms [illegible]

[illegible] (1947) believed that penicillin would replace fever altogether and, in Great Britain, Martin (1948) with 24 cases considered that the risk of fever was seldom justifiable Hahn *et al* (1951), with 589 cases treated, also advocated penicillin alone

[illegible] and Richards (1947), on an experience of 50 patients likewise recommended [illegible] (1951), after treating 52 cases of paresis, believed that combined therapy was best for severe cases

Rose and Solomon (1947), of Boston, combined three million units of penicillin with half a course of fever therapy (4–6 paroxysms of malaria above 104° F , or 20 hours in the fever cabinet at 105° F or above) Of 100 patients so treated, 75 with paresis, 62 were improved, 35 showed no change and 3 were worse Of 60 treated with penicillin and malaria 40 were improved and 20 showed no change These results were slightly better than those achieved by penicillin alone or by penicillin plus the fever cabinet

Reynolds *et al* (1946) treated 41 cases of dementia paralytica with or without fever (6–12 paroxysms of malaria within 40 hours in excess of 104° F) Penicillin alone improved 11 out of 24 and penicillin plus fever 10 out of 17 Weickhardt (1948), on an experience of 100 cases of paresis, likewise preferred penicillin plus fever The Boston group, Perlo *et al* (1951) reporting, finally admitted, however, on an experience of 469 cases, that penicillin alone *was* as effective as penicillin plus malaria

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(4) Penicillin, arsenic and bismuth

Parkhurst and Bowman (1948) reported on 458 cases treated by inducing fever with the Kettering hypertherm or by malaria, and with penicillin plus arsenic and bismuth They found that the augmented penicillin regime was superior to fever alone

Johnwick (1950), in a survey of 879 patients treated, could find no advantage in adding Mapharsen and bismuth to a schedule comprising 400 000 units of penicillin in oil wax daily for 15 days Leavitt (1947), having treated 171 patients with penicillin alone, or with penicillin plus oxophenarsone and bismuth, found possibly slightly better results with the latter method but these were insufficient to justify the extra risk involved

It is very doubtful whether the added risks attendant upon the use of either fever therapy or the arsenical drugs should even be considered today until after penicillin by itself has had a fair trial

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(5) Oral antibiotics

There is no advantage in treating a serious condition like neurosyphilis with oral penicillin when it can be given more surely by the intramuscular route

Aureomycin, chloramphenicol and terramycin have been tried in small scale [illegible]

Kierland and O Leary (1950) described the results of treatment of 12 cases The series presented by the same authors (1951) assessed the results of ten cases treated with 50–90 g of aureomycin and followed up for 122–573 days. It was considered that the results were as good as those obtained with penicillin

Five patients were treated with chloramphenicol by Romansky *et al* (1951) and [illegible]

by Meneghini and Sanguineti (1951) Those cases previously untreated fared best and chloramphenicol was found in the cerebrospinal fluid in three patients tested

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K [illegible]

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CHAPTER XI

CONGENITAL SYPHILIS

A. GENERAL

(1) Incidence

THERE has been a gradual fall in the incidence of congenital syphilis of all forms both in the U S A and in Great Britain (Fig 13), but, since the



FIG 13—TRENDS IN THE INCIDENCE OF CONGENITAL SYPHILIS IN CONTINENTAL U S A AND ENGLAND AND WALES

(*Ministry of Health, London, and United States Public Health Service figures*)

——— Continental U S A scale on left - England and Wales scale on right

FIGURES FROM WHICH GRAPH IS COMPILED

	U S A	*U K*		*U S A*	*U K*		*U S A*	*U K*
1941	17,592	1,380	1945	12,339	1,355	1949	14,295	1 417
1942	16,924	1,464	1946	12,106	1,382	1950	13,446	1,223
1943	16,173	1,727	1947	12,254	1 353	1951	12,836	1,127
1944	13,576	1,552	1948	13,309	1,407			

institution of routine serum tests for expectant mothers and the introduction of rapid effective treatments for those found affected, the decline has been [illegible]

example, there was only *one* known infection in 73,627 live births (*Social*

Hygiene News, 1950) The fall in morbidity and mortality due to congenital syphilis in Baltimore was recorded by Nelson and Struve (1952) In the clinics of England and Wales in 1951 there were only 156 new cases of congenital syphilis under one year of age, a greater fall having occurred

TABLE 8

CASES OF CONGENITAL SYPHILIS UNDER ONE YEAR OF AGE SEEN FOR THE FIRST TIME IN THE CLINICS OF ENGLAND AND WALES

1931	339	1941	223
1932	302	1942	245
1933	305	1943	310
1934	296	1944	346
1935	251	1945	326
1936	241	1946	363
1937	211	1947	343
1938	216	1948	372
1939	217	1949	355
1940	191	1950	227
		1951	156

in the immediately previous two years than in ten pre war years in the arsenic and bismuth era (Table 8)

That case finding, rather than treatment, is the important factor in the control of early congenital syphilis is evident from the mortality figures of

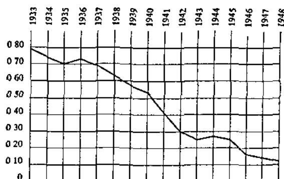


FIG 14—DEATH RATE FROM CONGENITAL SYPHILIS IN THE CONTINENTAL U S A

(Deaths under one year of age per 1 000 live births)

FIGURES FROM WHICH GRAPH IS COMPILED

1933	0 79	1939	0 57	1944	0 27
1934	0 74	1940	0 53	1945	0 25
1935	0 70	1941	0 41	1946	0 16
1936	0 73	1942	0 30	1947	0 14
1937	0 69	1943	0 25	1948	0 12
1938	0 63				

the U S A (Fig 14), which clearly show that the decline had set in well before the introduction of penicillin

For some reason the incidence of congenital syphilis in Africa, where in some parts the cases of early syphilis are numerous and the treatment given

Africans of 7 4 per cent due to syphilis Willcox (1949) showed from
... in preg-
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TABLE 9

MISCARRIAGES IN AFRICANS FROM SOUTHERN RHODESIA

	Patients	Pregnancies	Miscarriages	1–4 months	4–9 months	Percentage late
Rural	418	1,546	56	29	27	48 2
Urban	410	936	56	11	45	80 4

(2) Clinical

A review involving a life time of experience of congenital syphilis was
...

James (1951)

...

reaction in the humerus and tibia of a seronegative child of a one time syphilitic mother was presented as a possible case of cortical hyperostosis (Caffey's syndrome) by Dunlop (1951) Another such case affecting the ilium was described by Racely *et al* (1951)

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Negro children in the U S A and found teeth suggestive of syphilis in 69 Serum tests were performed on 53 of these and were positive for syphilis in 13 Beecher *et al* (1951) examined the teeth of 1,639 other American Negro children of an average age of 10 2 years Fifty-four children were

regarded as having teeth showing syphilitic hypoplasia Fifty of these were serum tested and positive results were obtained in 16 On the other hand in Africa, where the pattern of syphilis differs, Willcox (1949a) examined the teeth of 3,491 child Africans and 560 adults Only one person with a

A case of cold hæmoglobinuria in a late congenital syphilitic was presented by Suckling (1951), and another of the same condition, believed to be associated with gummata of the liver and lung, by Hill (1951) It was noted that the hæmolytic factor of this condition was distinct from the Wassermann factor and was thermostable The mechanism of hæmolysis in cold hæmoglobinuria was discussed by Jordan *et al* (1951, 1951*a*)

The difficulties in the interpretation of serum tests in infants born of mothers with suspected syphilis were clarified by Bundeson and Aron

time of treatment were seronegative 30 months afterwards, whereas 91 5 per cent of 38 patients who were over two years at the time of treatment remained seropositive

The value of having a note on the birth certificate as to the status of the prenatal blood test of the mother, as a starting point for the case finding of congenital syphilis, was emphasized by Ball (1951) Such data has been entered on birth certificates in South Carolina since 1945

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B. TREATMENT

(1) Prenatal syphilis

If pen...

The decline in the incidence of early congenital syphilis in the economically developed countries may be attributed partly to the routine serum testing of expectant mothers and partly to the rapid treatment with pen...

healthy infants Aron *et al* (1947) had only one infant which died, and one stillborn from cord prolapse, in those born of 36 syphilitic mothers treated with penicillin Bundeson *et al* (1950) claimed only six unsatisfactory outcomes in 203 such women Ingraham *et al* (1947) noted only two syphilitic infants of 41 born and remaining alive to 45 syphilitic mothers given 4 8 mega units of pen...

seven schedules of 600,000–2,400,000 units of penicillin (including one ...

... of syphilitic mothers treated during pregnancy with penicillin, and observed for 3 months or more, only 11 (3 5 per cent) were syphilitic

Likewise Speiser *et al* (1947) treated 259 pregnant mothers with one of six schedules comprising between 600,000 and 4,000,000 units of penicillin,

in one of which 8 injections of Mapharsen were also given Of the children born 95 per cent were not syphilitic Tucker (1949) treated 149 expectant syphilitic mothers with 0 6–5 0 million units of penicillin, some with Mapharsen and bismuth in addition There were only two abortions and one death—from sickle celled anæmia Of 146 live infants, 48 were seropositive at birth or during the first month of extra uterine life and two were seropositive for as long as 81–121 days Also Thomas (1949) stated that, of 450 syphilitic women treated with penicillin during preg nancy, only eight (2 4 per cent) produced syphilitic babies while the pregnancies of eight others ended in disasters not due to syphilis Shaffer and Courville (1951) reported on an even larger series of 631 syphilitic expectant mothers treated with penicillin From these there resulted only five living syphilitic babies one syphilitic neonatal death and one still birth A possible cause of the occasional failure is death of the fœtus resulting from a fœtal or placental Herxheimer reaction One such case, in which fœtal movements ceased within 24 hours of the onset of treatment was described by Bowen *et al* (1948)

Other work includes that of Olansky and Beck (1947) who contrasted the results of treatment with penicillin with those formerly obtained with intensive arsenotherapy Of 74 gravid females treated on the 5 day inten sive schedule the outcomes included one infant death from prematurity, four stillbirths and three abortions Among 49 others treated with penicillin and semi intensive arsenic there was one known stillbirth and one known abortion, and with 24 mothers treated with 2 4 mega units of penicillin alone there was one stillbirth and one abortion Wammock *et al* (1950) noted an unsatisfactory outcome in 12 4 per cent of 5 596 infants born to

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treating 300 syphilitic expectant mothers with penicillin, arsenic and bis muth There were only five abortions, ten stillbirths and ten deaths during the first year of life Apart from 14 cases in which the outcome was unknown, the issue of the remaining 261 was satisfactory The danger of treating pregnant women with neo arsphenamine, on account of encephal itis and other toxic neurological complications, was emphasized by Sturmer and Peters (1951) Fifty two pregnancies in syphilitic mothers treated with penicillin were observed by Ingraham *et al* (1948) There were 46 apparently healthy children, three abortions, one miscarriage at 5 months, one stillbirth and one premature infant This was not con

proved to have congenital syphilis

If the mother has already been treated for syphilis prior to conception

it is the practice in many clinics to give a further course of penicillin for the sake of the child during any pregnancies which may ensue during the next 5 years, however satisfactory the clinical status Though such a use of a non toxic drug as penicillin is without objection in these circumstances it probably is not actually necessary Goodwin and Farber (1948) watched [illegible]

[illegible] remainder.

Tucker (1949*a*) also deliberately withheld a second 'insurance' treatment with penicillin from 88 expectant mothers who had previously received penicillin for syphilis Although 30 of the mothers were still seropositive at confinement only one of 111 offspring was proved to be syphilitic

Further figures to illustrate that mothers previously treated for syphilis do not necessarily require more penicillin during subsequent pregnancies were presented by Cole *et al* (1950), and by Goodwin (1950) In practice, the giving of an additional course of penicillin during a subsequent pregnancy is regarded as a simple and harmless procedure which may occasionally prevent the mother from relapsing and thereby affecting the child

[illegible] born within [illegible], it was noted [illegible] owed the same general pattern as those in the mother but at approximately one third of the latter The most favourable transfer took place when the child was born 6–12 hours after injection

Two syphilitic pregnant women, treated with chloramphenicol by Robinson and Robinson (1951), were delivered of healthy babies

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(2) Treatment of early congenital syphilis

The general aspects of the management of congenital syphilis were discussed by MacFarlane (1951) Thirty five cases of established congenital syphilis treated in Germany were described by Paul (1950) Of 286 cases observed in Madrid by Pedraza and Amezaga (1950) there was a mortality of approximately 25 per cent

The results of penicillin treatment of infantile congenital syphilis have been most promising, although the recommended total dose continued to rise before stabilizing in the region of 100,000-200,000 units per kg of body weight Rose *et al* (1946) reported 36 cases treated with doses of 11,000-75,000 units per lb 32 responded well although reagin remained present in the blood for an average of 154 days in those receiving more than 20,000 units per lb , and for 260 days in those receiving less than this They recommended that at least 75,000 units per lb should be given in aliquot doses every 3 hours Platou and his associates (1947) reported 252 cases from five clinics treated with from 770 to 150,000 units per kg given over from 7½ to 15 days A satisfactory outcome was obtained in 74 per cent but the authors concluded that a total dose of at least 100,000 units per kg in 120 doses at intervals of 3 hours was necessary Barker (1948) considered that 50,000 units of penicillin G per lb , given in 120 doses over 15 days, was an adequate treatment for a child with early congenital syphilis Yampolsky and Heyman (1946) likewise reported good results in 32 cases treated

Rose *et al* (1949) reported on 52 patients followed up for 2 years or more after treatment with penicillin Forty-one were quite well but eight others, although clinically fit, still had positive serum tests From Canada,

Morgan (1949) described the results of treating 54 infantile cases with penicillin, or acetarsol, or both

As in the adult, a Herxheimer reaction may be encountered following treatment with penicillin Pardo and Tucker (1949) noted febrile Herx heimer reactions in 45 of 95 babies given this drug Of 16 children under six months of age treated with penicillin by Putkonen (1950), fifteen showed a febrile Herxheimer reaction, whereas only 2 of 26 congenital syphilitics under one year of age showed this phenomenon Fatalities do occur with treatment but these usually result from intercurrent disease, such as broncho pneumonia or gastro enteritis How far the initiation of anti syphilitic treatment is responsible for the contraction of these complaints in already debilitated infants is not known De Jong (1948) had one death from broncho-pne...

...ever, compared with 35 5 per cent in a control series treated with arsenic and bismuth

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(3) Late congenital syphilis

Yampolsky and Heyman (1946) after reporting good results in 32 cases of early congenital syphilis treated with penicillin, stated that in late con genital syphilis there was improvement in only one of nine cases of inter stitial keratitis, and in none of three cases of Clutton's joints, or in two of eighth nerve deafness Platou and Komentani (1948), on the other hand, treated 109 children aged from two to thirteen years (81 of whom showed clinical signs and 36 per cent had abnormal spinal fluids) with penicillin in doses up to 50 000 units per lb given every 2–3 hours over 7–14 days

Results which were clinically satisfactory were obtained in 81 6 per cent Of 52 patients under six years of age, 84 6 per cent became seronegative or showed a declining serological titre, but over the age of six the figure was only 58 7 per cent

Klauder (1947), in a lengthy paper, described the progress of 72 cases of interstitial keratitis treated with penicillin Results were never dramatic and the treatment did not necessarily prevent a later recurrence in the other eye Nine cases of interstitial keratitis treated with penicillin, with fever by T.A B vaccine in addition, were reported by London and Noojin (1948), who were not too enthusiastic about the results

Scheie (1950) reported improvement of vision in all of six patients with corneal opacities due to past interstitial keratitis, after corneal grafts had been applied

Cortisone drops of a 1 4 dilution of cortisone acetate were instilled hourly for ten days in nine cases of interstitial keratitis by Simpson *et al* (1951) Penicillin injections were given at the same time, and all but one showed improvement Two cases, each treated with cortisone locally, were reported by Horne (1951) and by Maddin and Danto (1951), and nine [illegible] (1951) Single cases were treated by Geddes [illegible]

As an alternative to drops, cortisone may be used economically by subconjunctival injection

Woods (1951) considered that, if cortisone was used before any necrosis of the cornea had occurred, the results were good and might be dramatic Five early and five late cases treated were reported by the same author (1951*a*) An encouraging report was made by Crane and McPherson (1951), who used cortisone drops on 17 eyes of 11 patients Subjective relief was noted in four days, and arrest in ten days in 16 of the 17 eyes There was recurrence once in eight eyes and twice in two eyes, but all of these responded to retreatment

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CHAPTER XII

THE TREPONEMATOSES

A. ENDEMIC SYPHILIS

ENDEMIC non-venereal syphilis has been known for years to exist in the Balkans, and the World Health Organization, in conjunction with the Yugoslavian Government, has been conducting a mass treatment opera- [illegible]

been examined Guthe *et al* (1952) stated that by the end of 1951 no less than 941,563 persons had been examined of whom 91,988 had been treated (See Table 10) The endemic syphilis of Bosnia Herzegovina of Yugoslavia was also considered by Ostertag (1950), and it has formed the subject of a special W H O monograph by Grin (1952) who has been actively concerned with the mass treatment work there (Fig 15)

Superinfection

Grin has noted that in areas where there are many gummatous lesions the incidence of early infections is high He believes that this combination indicates the freshness of the focus and that many gummata arise from *superinfection* in previously untreated latent cases

Gummata arise from allergy, either from internal or external treponemata The theory that gummata arise from superinfection has been discussed for years, especially by the French, but will gain more impetus from Grin s observations The same has been noted in yaws An infected child will cause a primary lesion containing demonstrable treponemes on the nipple of its mother if she is previously uninfected If she has had the disease herself for some years, a gummatous type of lesion may occur In other words the lesion of superinfection is related to the stage of the *first* infection (Fig 21)

Proof of the theory should be forthcoming from the venereal diseases statistics of the Health Departments of the world There was a peak incidence of early syphilis in many countries in the years 1946 and 1947,

since become extremely low and therefore the chance of superinfection has also been drastically diminished Thus, *if this superinfection theory is* true, one may expect no such rise in the incidence of gummata in the

TREPONEMATOSES

EARLY ORAL LESIONS



FIG 15—ENDEMIC SYPHILIS OF BOSNIA
(Dr E Grin Yugoslavia)



FIG 16—NJOVERA OF SOUTHERN RHODESIA

EARLY CONDYLOMATA LESIONS

FIG 17—VENEREAL SYPHILIS IN U K



FIG 18—BEJEL IN SYRIA (Dr E H Hudson U S A)





FIG 19—YAWS OF UGANDA
(Dr C J Hackett London)

FIG 20—NJOVERA OF SOUTHERN RHODESIA

FIG 21—DICHUCHWA OF BECHUANALAND 'THROWBACK' INFECTION
(Dr J F Murray, South Africa)



Note that lesion is of a gummatous type The mother had been treated one year previously with ten injections of neo arsphenamine for condylomata The baby had active dichuchwa which preceded the breast lesion See Superinfection, p 162

venereologically well developed communities, while in those parts of the world in which penicillin has not so far been used in massive amounts the incidence should remain high

Another area in which World Health Organization activity has been considerable is Iraq Here *bejel*, first described by Hudson as affecting the

000 of these had been 77)

the W H O operation in Iraq He considered that of the five million persons in the country one million have had, have got or will have the disease In serological surveys conducted in the Amara area seropositivity rates of 37–81 per cent were encountered Both Hudson and his successor, Csonka, rendered informative monthly reports to the World Health Organization Csonka (1952) published a short descriptive article on bejel, and other papers, more comprehensive, are expected (Figs 18, 26 28, 29)

Like the other treponematoses bejel is an endemic extravenereal disease of childhood caused by a spirochæte indistinguishable from *T pallidum* The primary lesion is seldom seen, but Akrawi of Baghdad (1949) inoculated ten human volunteers with infected matter from bejel, of these, eight persons developed primary lesions although no infections were induced in eight others suffering from general paresis Akrawi (1952) also presented three cases of 'throwback infection in bejel, in which the

areas,

These complications could have arisen however, from later attacks of venereal syphilis

Rizk *et al* (1951), in camera lucida and dark field studies could find no difference between the spirochæte of bejel and the spirochæte of syphilis Rizk *et al* (1951*a*) also described the successful intratesticular inoculation and passage of the bejel treponeme in rabbits

That other conditions of a bejel like nature exist in other parts of the world is also known Willcox (1949) described one such variety of endemic treponematosis in parts of Southern Rhodesia under the name *njovera*

other on each side

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B. YAWS

(1) Geographical

yaws-
British
aws in

Yaws in Brazil was considered by Guimarães (1950), in Columbia by Vargas Cuéllar (1941), and in Ecuador by J A M A (1941) Pardo-Castello (1939) described 500 cases seen in Cuba, and yaws in Venezuela was considered by Vegas *et al* (1943) and by Itriagos and Medina (1949)

Rutter (1941) described yaws in the Western Solomon Isles In a survey by Marples (1950), in Western Samoa, backed by the Medical Research Council of New Zealand, 32 9 per cent of 1,346 children examined were found to be suffering from this disease.

Yaws in the Bastar State of India was considered by Sen Gupta (1946), in Formosa by Takahashi *et al* (1940), and in Indonesia by Kodijat and Tuwahatu (1939) (*For other geographical particulars, see* Bangkok Yaws Symposium, p 170)

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(2) Clinical (Figs 19, 24, 25, 30)

The primary lesion of yaws was considered by Lopes (1945) and by Montel (1951) Secondary rashes were studied by Montel (1944) and the skin lesions of yaws by Hill *et al* (1951) Oral lesions of yaws were considered by Hackett (1939) and foot yaws by Charters (1945), Motta (1951) and by Jelliffe and H
si f yaws was con
an ntel (1949, 1950)
, between depigmentation and malnutrition was considered by Oomen (1952)
A
an
as
Fl
in yaws were described by Smith (1946)

Le Gac and Mulet (1950) considered goundou, while two other even rarer supposed complications, namely 'ghoul hand' and lymphostatic verrucosis, were reported by Jelliffe (1950 and 1951 respectively)

Owing to the prevalence of yaws in communities of primitive persons with a low standard of life, the disease is usually one of the darker-skinned races A case in a white American soldier was however quoted by Katzen

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(3) Investigatory

The interrelationship of syphilis, yaws and pinta was discussed by Hasselmann (1949, 1951), by Triana (1949) and by Weiss (1948) Gaps in the present-day knowledge of yaws were considered by Hackett (1949) and by Chambers (1950)

Superinoculation and reinoculation with yaws were considered by Guimarães (1946) Findlay and Willcox (1945) described a human experiment whereby a person who had been treated for yaws by one of them

of the syphilis-yaws group were studied by McLeod and Turner (1946) The differences noted were of degree and not of distinction Some resistance to further experimental infection with other members of the group was noted by Turner *et al* (1947) in rabbits which had been previously infected by *T pallidum*, *T pertenue* or *T cuniculi*

Contrariwise McLeod and Magnuson (1951) reported some interesting cross immunity experiments in rabbits with infections of yaws and syphilis of 7–10 months' duration It was noted that animals failed to

from three yaws and three pinta patients by Dillon and Cooper (1946) Flocculation and complement fixation tests in yaws were considered by

De Aquino (1950) and quantitative tests in Brazil by Ribas and Tavares (1950) Sepulveda and Ibarra (1949) used quantitative tests on 100 cases of yaws in the Philippines

The treponemal immobilization test has not so far helped in the differentiation of yaws from syphilis (Turner (1952)) The use of this test in yaws was described by Khan *et al* (1951) In the experiments of McLeod and Magnuson (1951) it was reported that there was a substantial amount of immobilizing antibody in the serum of rabbits with yaws which were not immune to further experimental infections with syphilis

The use of the phase contrast microscope to demonstrate *T pertenue*
lectron micro
were made by
Angulo *et al*
(1951) no differences in morphology and structure were noted apart from the lack of flagellæ on the yaws spirochaete—which finding was considered probably to be an artefact Many years ago Blanchard quoted by Hermans (1931) claimed to have seen with an ordinary microscope flagellæ on *T pallidum* but an undulating membrane without flagellæ on *T pertenue*

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(4) Treatment

Penicillin was first used in the treatment of yaws by Findlay *et al* (1944) on the Gold Coast since which time a number of writers have described

the use of this antibiotic, viz Arredondo (1951), Hasselmann (1951), Studenbord (1946), Tavares (1950), Guimarães (1950, 1951) in Brazil, Hill (1951) in Jamaica, Kivits (1951) in the Belgian Congo, and Rein (1949) and Rein *et al* (1950) in Haiti

Yaws is completely curable with penicillin in the doses normally given for syphilis, and procaine penicillin with aluminium monostearate (P A M) can give not only a reasonable individual cure but an excellent 'public health cure' with an economical single dose of 1 2 mega units This preparation has been tried in a number of single or few injection schedules

persons had been screened, of whom 57,598 were in an infectious state (Guthe and Reynolds (1951)) By the end of 1951 no less than 740,829 had been treated (Guthe *et al* (1952)) (See Table 10, p 17)

Rein (1949) assessed the results of the penicillin treatment of yaws in Haiti after a period of 12 months The initial healing of the lesions was dramatic and in 93 per cent the serological response was deemed satisfactory, but only 15 8 per cent had become seronegative Rein *et al* (1950) presented more detailed results Four daily injections of 600,000 units of P A M were given to 450 patients, 492 received the same dose twice daily for two days, and 258 were given 300,000 units twice daily for four days At the end of the year 787 of the 1,200 patients were re examined Clinical cure rates ranged from 94 to 98 per cent and serological improvement from 90 7 to 94 4 per cent In the later mass treatments in Haiti, Levitan *et al* (1952) reported not unsatisfactory results with a single dose of 600,000 units of P A M (given into the arm for speed) It is the opinion

by W H O in Indonesia and in Thailand By the end of 1951 no less than 1,112,236 persons had been examined and 226,170 treated in Indonesia, and 459,688 examined and 80,968 treated in Thailand (*Guthe et al* (1952)) (See Table 10) Facets of the Indonesian campaign have been described by Soetopo and Wasito (1952)

The oral antibiotics are effective in the treatment of yaws Ampofo

series to 7 and complete or near complete seroreversal was noted in two patients who had been followed up for six months Hill *et al* (1951) treated ten cases with 25 mg/kg of aureomycin daily for 14 days At one year six showed seroreversal and two others had a declining titre Loughlin *et al* (1951) also reported successful results with this drug on ten West

Indian cases each given 10 g The effect of aureomycin on the yaws treponeme was observed under the phase contrast microscope by Schaeffer *et al* (1951)

Chloramphenicol, in doses of 10 5–21 0 g given over a period of seven days, was used on four Gold Coast children with secondary yaws by Ampofo and Findlay (1950*b*) Rapid healing of the lesions was observed but, as might be expected, the serum reactions were still positive at six weeks Chloramph

esults by Payne
proved equally
Joseph (1951),
that these oral

Streptomycin is the least effective of the established antibiotics in venereal syphilis although it has some action (see p 16) Guimarães (1951*a*), however, obtained rapid healing of secondary yaws lesions with dihydro streptomycin

There have also been some recent papers concerning the older, now mainly discarded, methods of treatment Apted (1951) reported on the use of bismuth subsalicylate in Sierra Leone, and the use of bismuth was also considered by Scherpenhuysen (1948) The use of arsenicals and bismuth was considered by Apted *et al* (1948), S T B , a trivalent arsenical, by Kivits and Friedheim (1951), by Friedheim (1949) and by Ferreira and Pinto (1949), and a derivative of acetarsone by Ferreira and Pinto (1950) The use of chaulmoogra oil, a little used drug in the treatment of yaws, was described by Montel *et al* (1950, 1950*a*, 1951)

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7–90

(5) First International Symposium on Yaws Control

In March, 1952, the World Health Organization, jointly with The United Nations Children's Emergency Fund and the Thailand Government, held the First International Yaws Symposium at Bangkok Physicians interested in yaws, drawn from all over the world, attended and later took part in a field trip to North east Thailand to see the mass treatment teams in operation The papers presented at this meeting have been published by W H O , Geneva, W H O , V D Document 104 They include

Ampofo, O , and Findlay, G M , 'Preliminary Report on a Yaws Campaign in the Forest Region of the Gold Coast'
Bonne W M , Guthe T and Reynolds, F W , 'The Role of the World Health Organization in Yaws Control

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Guimarães F N , 'Yaws in Brazil'
Hackett, C J , 'The Extent and Nature of the Yaws Problem in Africa'
Hackett, C J , 'The Consolidation Phase of Yaws Control Experiences in Africa'
Hasselmann, C M , 'Unknowns in Yaws'
Hill, K R , 'Non specific Factors in the Epidemiology of Yaws'
Hill, K R , 'Antibiotics other than Penicillin in the Treatment of Yaws'

Huggins, D R, 'Teaching and Training Methods'.
Jungalwalla, N, 'Development of Plans of Operations'.
Keeny, S M, 'The Rôle of the United Nations Children's Emergency Fund in the Control of Yaws'.
Kitchen, D K, and Rein, C. R, 'Time-dosage Relationship of Penicillin Therapy with Special Reference to Yaws' (1) Laboratory Basis for Effective Therapy'
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Wasito, R, 'Comparison between Framboesia Prevalence in Two Villages'
Wasito, R, 'Pilot Project of the Treponematoses Control Project in East Java'
Wasito, R, 'First Quarterly Report on the Pilot Project in the Subdistrict Drijo'
Willcox, R R, 'Extent of the Problem in Africa Marginal Interests of Yaws Campaigns'.

C. PINTA (Figs 23, 35)

The more important references, 177 in number, up to the year 1942, were presented in a comprehensive medico-historical review by Holcomb (1942) Beerman (1943) published a review of the then recent ætiological and clinical studies Other general articles were presented by Herrejon (1945) and by Léon Blanco (1946) A comparative study of syphilis, yaws and pinta was made by Grau Triana (1949)

Pinta in Brazil was considered by Costa (1947), Guimarães and Rodr

s (1949), in Cuba

Ecuador, Lince

13 3 per cent of

tests were positive and 5 9 per cent were doubtful Statistics of the incidence of pinta in Ecuador were given by J A M A (1951) Pinta in Puerto Rico was described by Carrion *et al* (1941); in Mexico by Pequena

(1947), and in Venezuela by Rossi and Iriarte (1939, 1943) and by Iriarte (1940) Allen and Goodale (1946) described pinta-like lesions among the natives of Guam, and pinta in the Virgin Islands was reported by Fox (1939)

The transmission of *T carateum* to the rabbit was described from Cuba by Léon Blanco and Oteiza (1945) The results of experimental inoculations of infected material into human volunteers, whereby primary lesions were produced in the recipients, were considered by Leon Blanco (1948) Reinfection after cure was found to be possible, although superinfection in cases of late pinta could not be produced experimentally The primary lesion of pinta was reported by Leon Blanco and Laosa (1947), and the primary experimental lesion in Cuba by Oteiza (1945, 1949), and by Padilha Gonçalves (1949*a*) Experimental transmission was also considered by Padilha Gonçalves (1946) and Leon Blanco (1946) Gonçalves attempted experimentally to infect nine subjects suffering from yaws Two developed characteristic lesions of pinta at the site of inoculation but the seven others were unaffected It proved easier to produce experimental lesions in healthy subjects, thus indicating a partial degree of cross immunity Experimental lesions were cured by vanadium salts The possibility of insect vectors was well discussed in the review by Holcomb (1942) which included a reference to Leon Blanco (1941) who fed *Muscas hippelates* on serum containing *T carateum* and successfully transmitted the disease to a volunteer

Varela and Avila (1947) from Mexico, depicted the skin lesions of pinta on diagramatic maps, and stated that resolution of the lesions was only partial when the patients were treated with Mapharsen

The most hopeful drug for mass treatment is undoubtedly penicillin Rein *et al* (1951) reported 665 Mexican cases of pinta treated with procaine penicillin with aluminium monostearate Of these, 350 were followed up for up to two years and the results were excellent Single injections of 1 2 mega units proved sufficient for a mass campaign

Olarte (1949) considered the treatment of pinta with aureomycin, and Olarte and Varela (1948) used streptomycin

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D. TREPONEMATOSIS CONTROL

As matters stand today, with a high standard of life enjoyed by one fifth of the world, and a low standard of life by four fifths we must inevitably expect ...

... either by evolution or by design, but in either event has taken decades to assume its present form Treatment is based on the individual, and in areas (like the U S A) where the venereal disease control organization ... he individual with ... ien the numbers of ... finding but when found it is possible to give them the best available treatment

In the economically undeveloped areas, on the other hand, venereal diseases are common, in some places commonplace In addition treponematoses as endemic syphilis, yaws or pinta may affect tens of thousands Refined methods of control, with tracing of individual contacts and attempts at successf ... place and ...

... many other formidable companions as rivals, often superior rivals, to the treponemal diseases in the disease pattern of the countries concerned

Only a fraction of the national health budgets can be devoted to the spirochete Thus treponemal disease control in these areas is a matter of rough case finding by serum test and rapid clinical examination, or by none at all when whole populations are treated Treatment has to be

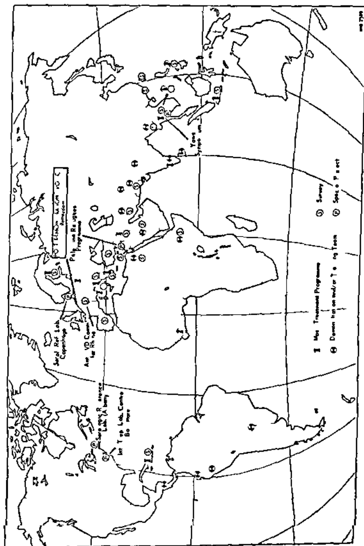


FIG 22—ACTIVITIES OF VENEREAL DISEASES AND TREPONEMATOSIS DIVISION OF WORLD HEALTH ORGANIZATION

(*Map prepared by World Health Organization Geneva*)

cheap and reasonably effective, aimed more at reducing the common reservoir of infection than at curing any one individual

Although treponemal diseases like yaws, pinta and endemic syphilis are not venereal, their causative organisms are, if not identical, closely



LATE PIGMENTARY LESIONS

FIG 23—PINTA OF CUBA
(Dr F Léon Blanco, Cuba)



FIG 24—YAWS OF UGANDA
(Dr C J Hackett London)



LA

FIG
MALAY
(Mr D
I



FIG 26—BEJEL OF IRAQ GUMMA OF NASAL SEPTUM
(Dr G W Csonka London)



LATE FACIAL LESIONS

FIG 27—NJOVERA OF SOUTHERN RHODESIA



FIG 28—BEJEL OF IRAQ
(Dr L G G Jones London)



FIG 29—BEJEL OF IRAQ
(Dr E H Hudson USA)



FIG 30—YAWS OF UGANDA
(Dr C J Hackett London)



FIG 31—VENEREAL SYPHILIS UK

related to *T pallidum* and they all respond to the same methods of treatment In the global activities of the World Health Organization against the treponematoses (Fig 22) it is mainly the syphilologists who have been enlisted to direct the campaigns From henceforth, therefore, these disorders *must* be included in any treatise of venereology

A more comprehensive viewpoint of the treponemal diseases has been taken by a number of writers including Hudson (1946, 1946*a*), Hermans (1950, 1950*a*), Willcox (1950), Guthe and Reynolds (1951) and Reynolds and Guthe (1951)

The methods used in the conducting of large-scale programmes were considered by Reynolds *et al* (1951) The various stages of a campaign were considered to be (1) Orientation and preliminary analysis of the problem, (2) Development of methodology, (3) Demonstration, Survey and Training phase, (4) Expansion phase (the mass treatment campaign), (5) Consolidation phase These phases have a considerable degree of overlap and throughout there is a gradual shift of responsibility from the aiding organization to the local governments who finally must accept the full load.

Guthe *et al* (1952) considered these matters further, and pointed out that it was essential that the P A M preparations with the economical dosage used in these campaigns must be up to standard, constant vigilance being necessary to ensure that the standard was maintained This matter has been clarified by the introduction of specifications by W H O for P A M preparations used by them These specifications are now listed in the International Pharmacopœia Ultimately the new diamine penicillin, Bicillin, or others like it will enjoy widespread use in mass treatment campaigns By ensuring an extremely prolonged serum level it will enable population groups to be 'simultaneously' treated without those so far untreated reinfecting those already treated

The establishment of primary control or pilot areas, aided by first-class laboratory facilities, is considered essential, so that the lessons learnt there can be applied in an unrefined manner to the countries as a whole It is also considered necessary to have as full a coverage of the population as is possible and to treat also the apparently uninfected contacts, lest those persons, who may be incubating the disease on the occasion of the first visit, would later reactivate the infection in the area (Fig 32)

What constitutes a contact has yet to be fully defined Some consider it to be the other members of the family in the hut or rondavel others the total population of the village May be as a compromise if all persons under sixteen years of age were treated in the infected areas, this measure would still be reasonably economical with penicillin The treponemal diseases are, after all, primarily diseases of childhood

Mass treatment alone, however, is not enough The initial gains obtained by the mass treatment bridgehead have to be consolidated by repeated further visits to the area at intervals of 6–12 months These measures ultimately have to be undertaken by the local health administrations, and

it implies, therefore, the establishment of permanent treatment facilities in the area

The treponematoses are diseases of the bush and jungle, and are only found on a large scale at the 'end of the road' With the opening up of an area they tend to disappear (being replaced by venereal syphilis) even without mass treatment schemes In many respects treponematosis control

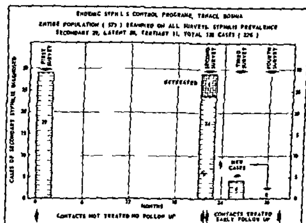


FIG 32 —MASS TREATMENT CAMPAIGNS VALUE OF TREATING CONTACTS

(Courtesy Venereal Diseases Division World Health Organization)

is like the control of a garden The treponemal weeds are killed in large numbers with penicillin, but unless periodic attempts are made to remove the seedlings, the area will soon become over run again If, after the initial clearing, subsequent revisits are regular and thorough, the disease may be kept down The permanent facilities established in the cleared area will then be available for other endemic diseases as well

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TABLE 10

PERSONS EXAMINED AND TREATED UP TO DECEMBER 1952 IN THE SIX MAJOR W H O/U N I C E F—ASSISTED PROGRAMMES

Programme	No Examined	No Treated
Haiti (yaws)	2 270 051	2 270 051
Indonesia (yaws)	3 529 831	533 587
Thailand (yaws)	1 679 342	216 047
Phil ppines (yaws)	415 000	24 000
Yugoslavia (endemic syphilis)	1 472 402	90,235
Iraq (bejel)	88 299	30 100
Totals	9 454 925	3 164 020

VENEREAL DISEASE CONTROL

A. GENERAL AND HISTORICAL

It is understandable, since the threat of war has not yet been dispelled, and there is danger of further venereological demobilization at a time when all of the control machinery may still be required in full, that some venereologists should stress the continued public health importance of these disorders

Thus Kitchen (1951) estimated that there are still 50 million cases of

in these schemes, of which one million had been treated with penicillin

Aufranc (1951) stated that, in the U S A in 1949, syphilis infected 150,000 persons (80,000 of whom were unaware of it), sent 6,000 to mental institutions, entered the blood stream before birth of 14,000 children and killed a total of 13,000 people It was estimated that over four million persons in the U S A would have shown a positive serum test Drolet (1951) reported that in 1945 there were 22,690 cases of syphilis and 18,000 cases of gonorrhœa in New York City In 1949 there were 20,489 cases of

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he venereal

Iskrant *et al* (1948, 1951)

'he venereo-
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venereologist

were also made by Lees (1950) The same author (1949) considered the question of teaching venereology to medical students

author (1951) considered venereal disease in relation to the Reports of the Poor Law Commissioners 1934–50 The treatment of the venereal diseases [illegible] of Samuel Cooper [illegible]

of Jonathan Hutchinson were considered by McKusick (1952)

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B. SOCIAL ASPECTS

Social aspects of the causation of venereal diseases were considered by Sutherland (1950) and by Willcox (1950) The relation of prevalence of syphilis to structure of the community was considered by Warner *et al* (1951), and the social aspects of venereal disease in Singapore were reviewed by Ram (1950)

[illegible]

This would lead to an increase rather than a decrease in the incidence of the venereal diseases He felt that the first aim, both from moral and

medical standpoints, should be to limit promiscuity, as even the most efficient contact tracing methods which are theoretically possible could never hope to reveal all of the foci of infection.

disease in the African in Southern Rhodesia were stated by Willcox (1949*a*) (Table 11)

TABLE 11

SOCIAL ASPECTS OF VENEREAL DISEASE IN THE AFRICAN

(Based on interviews of 100 African soldiers without venereal disease, and at least 100 Africans with venereal disease, in Southern Rhodesia)

	Non-Venereal	Venereal
Average age (years)	24 3	24 2
Married	40 0	24 4
Wives outside Southern Rhodesia	20 0	37 5
Those with children	32 0	14 5
Been to school	82 0	38 0
Speak English	61 0	23 0
Read and write	*81 0*	*50 0*
Two attacks of V D	8 0	35 0
Payment given for last intercourse	*26 0*	*97 0*
Could locate last consort	32 0	16 0

The psychiatric aspects of venereal diseases were discussed by Pahmer

(1949) studied patients having repeated infections with gonorrhœa and found that their intelligence was subnormal Venerophobia in the male was considered by Rogerson (1951)

Homosexuality relating to the venereal diseases was considered by MacDonald (1949) and also by Kanee and Hunt (1951) The higher incidence of venereal diseases in the uncircumcised was emphasized by Hand (1949) Venereal diseases as a cause of infertility were considered by Boyd (1949)

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C. VENEREAL DISEASES CONTROL IN VARIOUS PARTS OF THE WORLD

(1) U S A.

Control measures have been most intense in the U S A They were the subject of study of a special commission of the World Health Organization and a detailed report was made (W H O , 1950) American methods were inspected and summarized in three articles by Willcox (1946, 1949, 1951) The cost of venereal disease control in the U S A was considered by Clark and Carroll (1950)

Case finding

Progress in contact investigation was outlined by Stuart (1951) The most important arm of venereal disease control is *case finding*, and of case finding, *contact tracing*

investigation In females, however, contact tracing was responsible for 50 2 per cent of the cases found The same authors (1949a) reported that

Spoto and Iskrant (1949) reported on the results of contact tracing in syphilis in eight areas, and the results in 15 areas for the years 1944–1948 ha e also been p bl shed (Stat st cs (1949)) The n mber of contacts

· the numbers

index) from

ilis (brought

early syphilis

brought to treatment with syphilitic lesions (lesion to lesion index) from 0 06 to 0 19

The interviewing of contacts of syphilitic patients was considered by Sparks *et al* (1951) The use of a special form for the convenient description and tabulation of contacts was described by Fiumara (1949) The use of multiple-copy forms in contact tracing was considered by Eisenberg *et al* (1949) In the U S A every effort is made to trace contacts Steiger and Taylor (1947) reported the successful location of one woman, when the only fact known was that she had a five year old child in hospital with a broken leg

The rôle of the rural nurse in venereal diseases control, of which there are 7,000 in the U S A, was considered by Buck (1947) Case finding by the public health nurse was considered by Bulla *et al* (1951) Trautman and Giacomo (1949) considered the integration of public health nurses into the staff of a Marine Hospital

Baker *et al* (1948) adopted an unusual contact tracing measure in Chicago for gonorrhœa They refused to give any treatment to the infected patient until he had tried to bring in his contacts Of 244 patients so instructed 143 returned with their partners, the contacts of nine were verified as already under treatment, 34 returned to report failure and 32 others obtained additional information of use to the field workers Twenty six patients did not come back, but 14 of these were recaptured as a result of field work Only six were definitely known to have deserted the clinic for the private physician

Another method tried in Chicago was to notify the contacts of infectious

lt of send ng 1 541 telegrams Bauer *et al*

sexual contacts but towards other members of the same social circles as the infected patients Thus other members of bottle or brothel parties at which the patients had contracted their infections, and even merely promiscuous acquaintances, were all brought in and tested Richardson and Council (1947) reported that

no less than 822, or 22 6 per cent

ding is the *mass serum testing* of selected groups

Mass blood testing in Georgia was described by Bowdoin (1948) Gray *et al* (1948) reported on a four-month survey in the Mississippi Delta in which 399 plantations were surveyed, and 6,438 persons were clinically [illegible]

period Lamb *et al* (1947) reported that 7,777 patients were examined and 359 previously unknown syphilitic infections were revealed.

The majority of States now insist on premarital and prenatal serum tests for syphilis The finding of a positive blood test, however, does not necessarily mean that the patient is brought to treatment Plotke *et al* (1950), in Chicago, found that a letter sent to patients found to have positive blood tests secured only 32 per cent A visit by a social worker secured 49 per cent but, if both methods were employed, 62 per cent were secured

Contact tracing is expensive Crowley and Tucker (1947) calculated that it cost two dollars per person to bring in 1,111 contacts, but the cost proved to be 5 25 dollars for each person found to be infected The jewel of contact tracing—the primary or secondary syphilitic—however, each cost 63 93 dollars to secure The organization of venereal diseases cam- [illegible]

in a control county where no such project was in force they decreased by 40 per cent

Many cases of venereal disease are treated by the private physician, Heller (1947) estimated the number at 50 per cent Often the contacts of these cases are not properly secured as the physicians may send in no morbidity report

At Louisville, Kentucky, Lamb *et al* (1947) reported that free penicillin was offered to practitioners over a 45-day period on the condition that the [illegible]

previous year.

Turner (1950) described methods of arousing the practitioners' interest in reporting cases Sklar and Schuman (1949) devised a method of stimulating private physicians by following up the positive blood tests obtained in the public health laboratories At Topeka, Kansas, all positive blood [illegible]

Beelman (1947) reported that 146 proved to have primary or secondary syphilis

Case holding

With the introduction of rapid treatment methods with penicillin most

It remains, however, important to the individual if cure is to be fully assured

Of 103 cases of syphilis treated by private practitioners in Vermont Aiken (1949) reported that only 2 1 per cent failed to complete adequate treatment Even so the shorter the schedule the greater the number that complete it In Delaware the results of six , seven , eight and ten day

the other hand in Colorado, Sorenson and Shannon (1949) reported that nine out of ten patients completed a 20-day schedule

Usilton and Lugar (1951) emphasized the necessity for efficient case holding in research studies They reported that of 1,538 selected patients treated for syphilis no less than 89 6 per cent were still under observation at an average of 37 7 post treatment months

Propaganda and education

The value of education as a case finding medium was considered in detail by Morse and Iskrant (1951) The intent of the American Venereal Diseases Association which grew from the American Neisserian Society, was proclaimed by Barnes (1949)

Many novel methods of V D propaganda are used in the U S A , from the book match and brochure to the disc jockey and dirigible Education methods in Nebraska employing moving pictures and gramophone

It is difficult to assess how far such methods are successful for the results almost defy analysis A study was made by Wright et al (1950) in North Carolina of gonorrhœa cases in Negro veterans (ex service men) and Negro civilians to see whether there was any significant difference in the two groups as to the duration of the discharges before the patients reported to hospital It was suggested that the ex service group sought treatment the earlier as a result of education acquired in the Army

America differs from European countries in that it has a large Negro

most from pamphlets or papers, 0 6 per cent only from the radio while 40 per cent learned most from motion pictures exhibited in the venereal diseases clinics

How far case finding measures have themselves been successful in reducing the common pool of infectiousness it is difficult to say Certainly

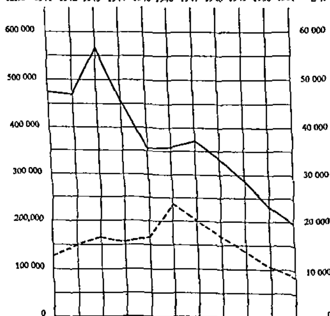


FIG 33—POST WAR DECLINE IN INCIDENCE OF SYPHILIS TOTAL SYPHILIS IN CONTINENTAL U S A AND ENGLAND AND WALES

FIGURES FROM WHICH GRAPH IS COMPILED

	U S A	*U.K*		*U S A*	*U K*		*U S A*	*U K*
1941	477 841	12 762	1945	356 315	16 642	1949	288 769	13 699
1942	472 245	15 071	1946	360 918	23 878	1950	231 567	10 967
1943	564 920	16 750	1947	373,296	20 137	1951	198 640	8 432
1944	458 199	15 918	1948	338 141	17,129			

the death rate from mainly late syphilis has declined from 15–16 per 100,000 population in 1933–1939 to 7 0 per 100,000 in 1950 (Wright, 1952)

Heeren *et al.* (1950), speaking of North Carolina, felt that case finding measures had not so far succeeded, as there was no appreciable lessening in the numbers of positive results in the prenatal and premarital blood tests

[illegible]

methods are voluntary, and often limited to the use of the contact slip (Fig 33) Certainly by comparison with the huge American contact tracing plant the British machinery is puny It is likely that the decline in incidence is due to the use of penicillin for other diseases Penicillin given for gonorrhœa, penicillin given for a sore throat, penicillin given for a septic finger will, in some people, abort a developing syphilitic infection without the patients ever being aware of it It may well be that the general practitioner, with his mass use of penicillin, has quite unwittingly played the major part in syphilis control

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(2) Europe

Venereal diseases in post war *Germany* were considered by Guthe (1949) and by Harding (1950) With the setting up of venereal diseases hospitals in the U S zone of Germany, De Forest (1950) reported a decline in incidence of from 30 per 10,000 in 1946 to 11 2 per 10,000 in 1949, while the figures for gonorrhœa in the same years were 90 and 23 per 10,000

France by Durel (1951)

Volosceanu (1948) reported the results of mass serum testing in two districts of *Rumania* In two large groups of 101,690 and 119,844 persons respectively there were 4 06 and 4 26 per cent of positive results This is ten times the annual incidence of syphilis in the British Navy (4 06 per 1 000 in 1948) as reported by Belcher (1949) The contemporary male defaulter in *Britain* was considered by Horne (1950)

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(3) Africa (see also Neurosyphilis, p 138)

Guthe (1949) reported on venereal diseases in Ethiopia Soto (1949) described a venereal diseases campaign in Morocco

O'Malley and Wilson (1949) performed a serological survey on 1,000 natives reporting from their tribes for work in Cape Town Some 7 4 per cent of positive and 3 8 per cent of doubtful tests were recorded Willcox (1949), with the help of a mobile laboratory, spent six months in conducting a venereal diseases survey of the African in Southern Rhodesia Facts relating to the incidence of syphilis, gonorrhœa, soft sore, lymphogranuloma venereum and granuloma inguinale, together with a consideration of local habits and conditions, were reported The same author (1950) related an unusual event in contact tracing when a polygamous husband brought 28 of his family to the clinic by bus (Fig 34)

McKay (1950) undertook a field survey amongst the Masai of Kenya Venereal diseases in the British Colonies were considered by Rae (1951), McElligott (1951) and Lees (1951) Gonorrhœa in West Africa was considered by Clarke (1951), and venereal disease in British West Africa by Willcox (1946)

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(4) Others

References to control measures in yaws, pinta and endemic syphilis are considered under Treponematoses (Chapter XII) World statistics of the



FIG 34—CONTACT TRACING IN AFRICA

The man was asked to bring his family for examination This he did in his own bus He had 6 wives and 25 children, and one other in embryo See p 188



FIG 35—KAALKOP
See p 87
(Dr J Marshall South Afr ca)





36—A PORTION OF *T CARATEU M* OF PINTA × 36 000 UNDER THE ELECTRON MICROSCOPE See p 167
(Dr G Varela Mex co)

numbers of cases (where known), and the deaths registered as due to syphilis, have been compiled by the World Health Organization (W H O, 1952)

in the Ghund area of the Himachal Province, *India* This was a high prevalence area for only 22 6 per cent of 354 families examined had no member with syphilis The community was treated, for reasons of economy, with only 300,000 units of P A M for each person This measure was considered to have reduced the reservoir of infection

An account of the spread of venereal syphilis in a *Greenland* community of … 19, 1950) In five
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D PROPHYLAXIS (see pp 23 and 108)

Compulsory treatment of infected women in Batavia led to a marked initial fall in the venereal diseases rate in soldiery, although this was not

(1949)

Mahoney (1947) announced the Guatemala project on a 'relatively fixed population' and indicated that certain experiments were to be undertaken in the prophylaxis of gonorrhœa and syphilis The results of this have not yet been fully published

Eagle *et al* (1947) showed that the amide substituted phenyl arsenides

that it gave full protection against experimental syphilis of the rabbit

A somewhat controversial subject is the prophylaxis of the venereal diseases by chemotherapy, or more correctly by 'abortive treatment'

In Mexico in 1949 a prophylactic campaign was commenced by giving 300,000 units of penicillin G in oil to all who were venereally suspect Gooden (1950) reported a considerable decline in incidence amongst the personnel of a local naval garrison as a result

Eagle *et al* (1948, 1949) divided 350 naval personnel into two groups, half acted as controls and the remainder received oral penicillin immedi-

ks there were

1,000 shore

)00) *in those*

receiving 100,000 units of penicillin in a buffered tablet The dose was then increased to 250,000 units and in the next eight weeks there was only one

given earlier Experiments in prophylaxis with oral penicillin have also been performed on British Service personnel overseas The full publication of results is awaited with interest No papers have yet appeared concerning the results of prophylaxis with the oral antibiotics but there is every reason to believe that they are equally successful

disease than the larger numbers who do not

Medically too there is the fear of incompletely cured gonorrhœa and masked syphilis The aphorism 'Diagnosis precedes treatment' is often

the normal period of observation, i e

period or fairly quickly shows itself

The prophylaxis of venereal disease by condom, ointment or urethral irrigation *has been practised for years* The suppression of a disease by abortive treatment was accepted for thousands as necessary for the preven tion of malaria in war-time, so no new *medical* principle is involved The

kely to be sustained indefinitely, for
use a condom he can be advised

Although its use for troops stationed overseas may be limited by expense, it is felt that the chemoprophylaxis of venereal disease will ultimately be widely used by individuals when the risks that have been taken justify it, and especially when there are possibilities of transferring disease further without it (e g for married men after a regretted episode)

The alternative is the observing of the anxious patient for a period of three months, during which time repeated serum tests are performed While many may feel that any anxiety present is not the fault of the doctor, all will agree that few patients actually complete the prescribed three

The drugs which are effective, however, can in Great Britain only be obtained by means of a prescription from a doctor The writing of such prescriptions in advance before promiscuous intercourse would be unacceptable to most physicians and, therefore, abortive treatment is

this substance, it is a matter for speculation as to whether the limits of technical effectiveness of repository penicillins have yet been reached Perhaps, one day, a permanent antibiotic umbrella against the accidents of venery may be ensured by just a handful of injections each year

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